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Division of Computer Research and Technology

Fiscal Year 1980

Annual Report

Volume I

DCRT

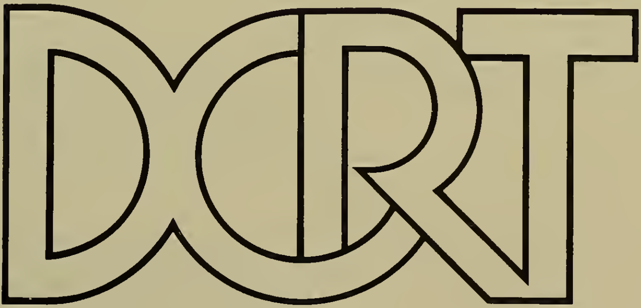
Division of Computer Research and Technology

Oct. 1, 1979
through
Sept. 30, 1980

Summary

Annual Report

Volume I



Foreword

The work of the Division of Computer Research and Technology covers a large spectrum of activities. It ranges from doing research in biology, statistics, mathematics and computer science to providing computer facilities and services for the NIH.

The several parts of DCRT embody and integrate this variety of talents. Each part has a major functional focus. But the success of the Division's work arises from the interaction of the members of each group with others across organizational and disciplinary lines. Many projects in the Division require the expertise of people from several segments of the spectrum.

DCRT's collaboration links our staff to professionals inside NIH and also outside NIH. The result is a balance in emphasis to provide the work done by DCRT at NIH with the benefits of collaborations outside of NIH. While DCRT does not have money for grants, it does provide occasional support for meetings on scientific topics related to its work.

This year our story starts with the service end of the spectrum and moves to the research end, presented in two volumes:

Volume 1 gives a summary overview of the work of each group and highlights its accomplishments.

Volume II includes detailed projects and activities of each group.

If you have comments on the report or suggestions for improving future versions, please send them to:

DCRT Information Office
NIH Building 12A, Room 3027
9000 Rockville Pike
Bethesda, Maryland 20205

From the Director

The Division of Computer Research and Technology (DCRT) was established in 1964 to make a then-emerging computer technology useful to NIH biomedical research and administration. Over the years, the work of the Division has indeed become integral to the conduct and management of the NIH research programs. It is a pleasure to report the accomplishments for FY1980 of an exceptionally competent and productive group of DCRT laboratories, branches, and offices and of the people that work in them.

The several complementary functions within DCRT support laboratories and clinics throughout NIH in a wide range of activities, as an essential part of the core of the NIH intramural scientific programs. Our independent biomedical research and technical development keep pace with advances of the times.

Computer use by NIH scientists and administrative staff has grown from exploration of emerging technology to innovation and leadership in information processing techniques across many fields. Only the combination of talented people and capable machines can cope with the vast amounts and varied types of computing at the NIH.

The essential challenge facing the Division and the NIH is to maintain continuity and to increase sophistication in computing in the face of constant change. Biomedical research is always exploring new fields, developing new investigational techniques. Computer science and technology are also dynamic fields, producing new machines and computer software techniques.

The constraints of the Federal personnel and procurement systems are an additional challenge. During FY80 the DCRT has been fortunate to retain highly skilled, experienced, and dedicated staff in the face of an extremely competitive national labor market in computer scientists and electronic engineers. Hiring appropriate people from this market is often difficult under Federal procedures and shifting personnel ceilings.

The complexity of Federal procurement procedures has in fact delayed getting new, more powerful, less expensive computers for the NIH Computer Center. But hard work by DCRT technical staff and the DCRT Office of ADP Policy Coordination during the past year has made it possible to maintain a responsive level of service on the NIH central computing facilities and has moved the necessary procurements into the forseeable future.

DCRT looks forward with enthusiasm to the coming year as an opportunity to work with NIH scientists and administrators in the creation of still more powerful and civilized computing systems. Equally important is the opportunity to build stronger intellectual links between this technology and the substance of science and the art of administration at NIH. After 16 years the frontiers of computing remain open for new advances in all NIH programs.

Arnold W Pratt

Arnold W. Pratt, M.D.

Director

Division of Computer Research
and Technology

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The Computer Center Branch designs, implements, and operates the NIH Central Computer Utility and its associated online telecommunications facilities in support of scientific and administrative programs. Joseph D. Naughton heads this largest component of DCRT.

Computer Center Branch

Joseph D. Naughton, Chief

Functions

The Computer Center Branch designs, implements, and operates the NIH Central Computer Utility and its associated online telecommunications facilities in support of scientific and administrative programs. The nucleus of the Computer Utility consists of two large multi-computer facilities, the IBM System 370 and the DECsystem-10. Communications facilities link these two subsystems and connect them by telephone lines to terminals of various types located in research laboratories and administrative offices throughout NIH.

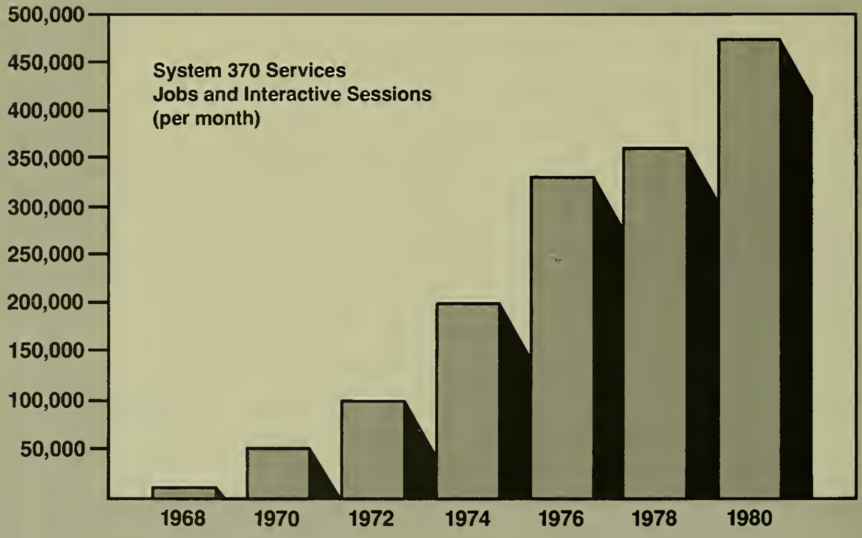
This computing and communications equipment (systems hardware) is complemented by a complex set of computer programs (systems software), which either are designed and implemented by Center personnel or acquired from other sources and adapted, to meet the unique requirements of the NIH biomedical research program.

Professional, technical, and administrative support personnel provide the many services available at the Computer Utility and ensure the smooth functioning of the total system 24 hours a day, 7 days a week.

Hardware and software aspects of the Computer Utility are maintained and controlled by the 139 members of the Computer Center Branch. The professional staff — 51 computer specialists, programmers, and systems analysts — provides the expertise to design and implement the complex computing systems; they supply extensive training and information services, assist users in problem diagnosis, and maintain and schedule recurring production applications. The 78 technicans operate the computer systems and auxiliary equipment and provide data entry services. The remainder of the staff gives the necessary administrative support.

In addition to operating the Central Computer Utility, the Computer Center Branch provides systems support, programming, consultation, documentation, training, and program support. A variety of programming languages are available, including FORTRAN, COBOL, PL/I, SAIL, and Assembly Language. The Center also maintains a data base/ data management system (IMS) and a comprehensive library of utility programs.

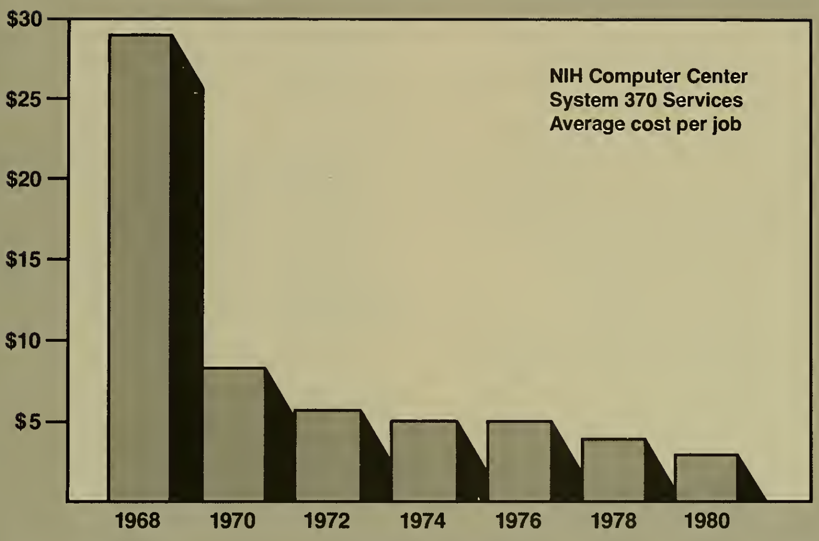
A number of interactive systems — such as WYLBUR, TSO, and the timesharing services of the DECsystem-10 — facilitate the creation, submission, and output of jobs and permit direct interactive computing using FORTRAN, BASIC, CPS, APL, MLAB, and other languages. The Center provides several facilities for the output of textual and graphic information on paper and microfiche. Programs to show two- or three-dimensional pictures on cathode ray tube displays and "sketch pads" for advanced graphic projects such as those involving macromolecular structures are also available.



Scope of Work

The NIH Computer Utility provides services to over 6,000 users including research scientists and program managers from every area of NIH as well as users from 24 other Federal agencies, in its role as a Federal Data Processing Center (FDPC) for Biomedical and Statistical Computation. All services are provided on a cost-recovery, fee-for-service basis through the NIH Service and Supply Fund.

Through the years, the workload of the Computer Utility has increased steadily. In FY1980 the Utility processed at least 11,000 mainstream jobs per day, completing 80 per cent of them within one hour. The 1800 remote terminals located throughout the country were the source of an additional 6,000 interactive sessions per day. Use of the IBM System



370 grew more than 11 per cent during the past year; the system reached its peak in April when it processed 481,249 job-sessions.

The DECsystem-10 timesharing facility continued its steady 10 per cent growth rate and reached saturation early in the fiscal year when it was processing over 12,000 sessions per month.

Research continued in the areas of text editing, application utilization of mass storage devices, display of biomedical objects, computer networking, and communications.

Highlights of the Year's Activities

The past year has been a significant one with many projects that have been underway for years approaching completion.

- The long-awaited reprocurement of improved hardware for the Computer Utility made progress. The contract for the new Timesharing facility was awarded; Digital Equipment Corporation delivered a new multi-processor KL10 system as the year came to an end. An interim upgrade — a new, faster 3033 MP CPU (Central Procrossing Unit) for the IBM System 370 — was approved and installed. Bids were received for the replacement of the entire IBM System 370 facility, with contract award anticipated by the end of the year.
- An IBM 3850 Mass Storage System (MSS) was installed to meet the growing need for readily accessible, online data storage space. Capable of storing over 2000 billion bytes of data online, the MSS increased both the effectiveness of the NIH Computer Utility and the productivity of the Operations Staff.
- Major advances were made this year in the development of New WYLBUR. Software, documentation, and internal testing of all of the modules was completed. Final integration testing was begun.
- The most significant monitor upgrade since 1974 was tested and installed on the DECsystem-10. The new operating system, called 7.01, increased system efficiency and reliability and provided a few new commands and system programs. In the upgrade most I/O (input/output) handling routines were rewritten completely, unlocking performance potential that was unavailable under the system configuration of the old 6.03 monitor and giving users a dramatic improvement in system capacity and response time.
- The molecular graphics system was used in the development of a new package of images, called TAMS, for teaching macromolecular structure. Dissemination of the package to 500 biochemistry departments in universities and medical schools throughout the world resulted in a heightened interest in computer graphics as a tool for the representation of macromolecular structure.
- Major reconstruction efforts in Buildings 12 and 12A got underway during the year. The building renovation program, initiated several years ago, provides additional space for arriving new equipment, as well as improved security and convenience for users. Innovations include a new, spacious, User Terminal Room and conveniently-located, computer-controlled, locked output boxes which will ensure privacy and faster distribution of user output.

Future Plans

The Center expects a challenging year as it continues its efforts to provide users with improved services.

After many years in the making, New WYLBUR, a greatly improved version of the popular text-editing program will be in full production use. New WYLBUR will provide users with many new editing capabilities and greatly enhanced document formatting, including automatic pagination and generation of headings, footings, tables of contents, and indices. The new system will also offer automatic recovery after line disconnect or system failure, as well as other performance improvements and new features.

With the arrival of the new System 370 equipment expected early next year, the rapid, efficient installation of hardware and software for the system will be a major priority. Implementation of the new equipment and completion of the building reconstruction will be important steps toward the goal of continuing to provide users with the best available tools for biomedical and statistical computing and the finest in turnaround and support.

Work is underway to redesign and improve the Center's printing capabilities while reducing printing overhead and manpower requirements. New equipment is being integrated into the system and older functions are being phased out in order to provide easy-to-use printing facilities that produce work of consistently high quality. The new facilities will provide expanded character sets, user-supplied character sets, and improved forms capabilities.

Providing full utilization of the capabilities of the recently-acquired mass storage system will be an important priority in the coming year. The current goal is an implementation proposal to determine how the capabilities of the mass storage system can best be developed to meet the special needs of the users of the Utility.

Improving the reliability, availability, and performance of the Computer Utility is a continuing goal of the Center. To this end, the coming year will see the extension of service hours and the implementation of a number of system improvements. To enhance teleprocessing services, the telecommunications link between the DECsystem-10 and the System 370 will be strengthened and improved; new features including networking services, teleprocessing diagnostic facilities, automated fault detection, and screen editing capabilities will be implemented for communications based services. Other projects planned for the coming year will provide better support facilities for remote users, improved scientific functions, and simplified data handling and management techniques.

Publications

Bina, M., Feldmann, R. J., and Deeley, R. G.: Could poly(A) align the splicing sites of messenger RNA precursors? *Proc. Natl. Acad. Sci. USA* 77: 1278-1282, 1980.

J. Emmett Ward heads the Data Management Branch. DMB staff design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific, and management data processing problems encountered at the NIH.

Data Management Branch

J. Emmett Ward, Chief

Functions

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design, and programming. There are currently 47 permanent full time employees whose disciplines include computer science, mathematics, and statistics.

Scope of Work

DMB staff design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific, and management data processing problems encountered at the NIH. Each new computer system user is provided comprehensive training in all system facilities and functions. In addition DMB staff teach courses about data management and DMB programming tools; they provide advice on data management techniques to NIH programmers; they serve as consultants to the B/I/D's for obtaining and monitoring contracting services for computer systems development; and they create and maintain general purpose, user-oriented programming tools to speed building and improve operation of applications systems.

The DMB comprises six sections. The **Applied Systems Programming** Section (ASPS) and the **Scientific Applications** Section (SAS) provide general computer systems analysis and programming services for all of the BID's. The ASPS supports general data management, and the SAS handles those projects which require scientific data analysis.

The **Data Base Applications** and **Data Base Enhancement and Control** Sections develop and maintain the central administrative data base for NIH materiel and financial management. The **Clinical Support** Section develops and maintains the Clinical Information Utility as a data base for research and patient care in the Clinical Center.

The **Software Support Section** designs and develops or purchases software development tools and programming aids and provides maintenance and training support for these facilities.

FY80 Accomplishments

At the beginning of the fiscal year the Data Management Branch was advised by the NIH Office of Administration that the original agreement to add five people to the administrative data base development team could not be honored due to personnel shortages. This loss alone will extend the estimated development period by about fifteen months, but it was felt that most of the key aspects of materiel and financial management could still be functioning in a data base environment by the end of calendar year 1981.

In December, 1979 and January, 1980 the additional loss of software development and user liaison personnel also slowed progress on the existing data base effort and caused the DMB to reexamine its priorities and to make some organizational and personnel adjustments. The Documentation and Systems Support Section was abolished and its personnel were absorbed by the Applied Systems Programming Section (ASPS). This enabled the Branch to shift two people from the ASPS to the administrative data base effort. Approximately four months were lost due to project reassignments, personnel shifts, and organizational adjustments, but without these changes the data base project would have been in serious jeopardy.

In spite of these setbacks major progress has been made in this key area. Partial payment of line items on an order and generation and control of payment schedules that go to Treasury were implemented in the middle of the fiscal year. A pilot test of delegated procurement entry utilizing teletype-compatible terminals has been started with the Division of Cancer Treatment, NCI and, if successful, should be completed by the end of calendar year 1980. This first important step will eventually permit BID point-of-transaction data entry for all delegated procurement and receiving actions.

Basic purchase agreements and indefinite delivery contracts require monitoring and control to achieve overall fund control. The software development effort for these functions was completed during fiscal year 1980 and is scheduled to be implemented as fiscal year 1981 begins.

The data content of the NIH Clinical Information Utility was broadened to include vital signs, blood bank, radiology, and nuclear medicine in addition to the laboratory test and demographic data. The Data Management Branch is participating in Clinical Center committee meetings concerning reduction in size of the medical record and future plans for computer based support to NIH clinicians. As an initial trial for automating and reducing the size of selected segments of the medical record, a system was developed to produce cumulative laboratory results on a weekly basis.

In addition to this work on central data management facilities, the significance and breadth of DMB's involvement in the NIH mission is depicted by the multiplicity of computer systems it has developed to support individual scientific, administrative, and management projects during the past year. Virtually every BID has benefited from the computational service provided by the DMB. Each of these systems has served a vital segment of the NIH and when viewed as a group represent the DMB's very reason for existence.

In the area of general support the DMB continued to maintain and teach courses on the Inquiry and Reporting System (IRS) and MARK IV; to support NIH use of Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS) awareness searches on a biweekly and semimonthly basis, respectively; to consult and assist NIH programmers and contractors, enabling facile use of DCRT computer facilities; and to maintain and distribute the NCI Survival System.

Future Plans

DMB intends not only to continue its primary role as a central NIH resource, but also to improve the facilities that it offers. Such things as voice input and answerback are being examined for their potential in specific applications areas. New capabilities in file and data base management systems are always being reviewed and improvements in existing systems for data retrieval and analysis are planned.

The Clinical Support Section (CSS) will concentrate on integrating the various independent files in the CIU to facilitate data displays, data analysis, and subfile creation. Collaboration with the Clinical Center to automate and thus reduce the size of selected segments of the medical record will continue. The CSS will examine alternative methodologies for providing routine data analysis facilities and will attempt to define other options for non-routine analysis.

The accounts payable, delegated procurement entry and inventory functions should be added to the administrative data base in the next fiscal year. In addition, design of the requisitioning and general ledger modules should be completed by mid-FY81, and DMB will be actively involved in specifying and developing these two functions by fiscal year end.

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McKinney, R. W., Pelham, V. F., Hellman, A.: Medical Surveillance Program of the National Cancer Institute. *Proceedings of 3rd Annual Symposium on Computer Applications in Medical Care*. IEEE, 1979.

Van Hoff, D. D., Layard, M. W., Basa, P., Davis, H. L., Jr., Van Hoff, A. L., Rozencweig, C., Muggia, F. B.: Risk Factors for Doxorubicin-induced Congestive Heart Failure. *Annals of Internal Medicine*, Volume 91, No. 5, November 1979.

Part of the work of the Computer Systems Laboratory centers on the investigation of applications of microprocessor technology to laboratory data acquisition and control and to the development of new biomedical and clinical instrumentation. CSL (left to right) electronics engineer Ronald Fico discusses one such project with Section Heads Arthur R. Schultz, Jr. and Daniel Syed.

Computer Systems Laboratory

Alan M. Demmerle, Chief

Function and Scope of Work

The Computer Systems Laboratory, a group of about 30 professionals representing the disciplines of engineering, computer science, medicine, and chemistry, is the major source of expertise at NIH for minicomputer and microcomputer technology. CSL engineers and scientists, in collaboration with NIH laboratory and clinical investigators, apply this technology in the areas of laboratory automation and patient care. Most work supports intramural research programs, although some projects have been undertaken with extramural programs and, more rarely, with other Federal agencies. In addition to supporting ongoing research, CSL also investigates new applications of computers to biomedical research and identifies appropriate technology for use in these applications.

Small computers that can be used in the laboratory or at the patient's bedside are increasingly important to biomedical and clinical research because of more and more complex research methods and instrumentation. Laboratory automation, data acquisition from analytical instruments, and patient monitoring are examples of functions to which CSL has applied small computers at NIH. Computers may be used only in an adjunctive manner, for example, as a more convenient means to acquire laboratory data; or they may be integral parts of an elaborate instrumentation system such as a computer-controlled mass spectrometer.

Recent technological advances are contributing to changes in the nature of CSL's work. Foremost among these advances are developments in large scale circuit integration (LSI)—the microprocessor revolution—that have brought about the miniaturization of computer components and a dramatic decline in their prices and power requirements. One result has been a greater availability of computers for biomedical research. Thus, CSL engineers are now able to use microprocessors to solve problems that once were avoided because of cost, size, or manpower constraints.

The Laboratory brings together professionals with diverse backgrounds to apply computer technology effectively to NIH programs and to offer research and development capabilities responsive to NIH needs. Engineers, computer scientists, and mathematicians evaluate and apply new electronics and computer technology to solve biomedical problems. Personnel with backgrounds in medicine, biology, and chemistry communicate effectively with biomedical investigators and clinicians and identify potential computer applications. This multidisciplinary approach aids the recognition of problem areas that will benefit from automation and the interpretation of research needs in terms of computer methods.

This year, CSL engineers and scientists worked on approximately 26 projects, representing collaboration with almost all of the Institutes. Most of these projects were continued from previous years; seven projects were begun this year. Projects range in size from consulting activities of a few days or weeks duration to large scale efforts taking a number of man-years. Because much work involves the development of new methods or technology, or is influenced strongly by the changing needs of research, it is often difficult to predict the long term scope of a project.

FY80 Highlights

Most CSL projects begin in direct support of NIH research programs and involve collaboration with investigators from one or more Institutes or Divisions. A case in point is a project between the Biomedical Engineering and Instrumentation Branch of the Division of Research Services and CSL to develop an automated electron microanalysis facility for elemental analysis of biological specimens. Started in FY79, this project received funding from several Institutes for capital equipment purchases. Investigators from the sponsoring organizations and from several other Institutes are planning research projects that will use the facility.

The system includes a 200 key scanning transmission electron microscope, a 50 key electron microprobe, and a PDP-11 minicomputer. The facility will be equipped to perform electron energy loss spectrometry and both energy and wavelength dispersive x-ray spectrometry. The computer will monitor, display, and store experimental parameters to facilitate repeating an experiment. Furthermore, it will perform online acquisition and analysis of data signals from the two microscopes. The signals include the outputs of the several spectrometer attachments as well as various electron current signals which result when the electron beam strikes the specimen. Each signal contains information relating to the elemental composition of the specimen.

Projects that are characterized by the need to handle numerous signals, large quantities of data, timesharing of several simultaneous tasks on one computer, or particularly complex signal processing often take several years from inception to completion. For example, the electron microanalysis project required that literally dozens of signals be interfaced to the computer. Interfacing hardware had to be purchased, input/output drivers had to be designed and written, and system software had to be developed to acquire and process each signal. All of this work must be coordinated with the preparation of application software to implement specific experiments.

By contrast, when goals are more limited, projects can often be completed in a few weeks to a few months. Microprocessors are used to advantage for these smaller projects to accomplish objectives that were once precluded because minicomputers were too costly or special purpose instrumentation was unduly complex. This year, a microprocessor system was developed for the Laboratory of Kidney and Electrolyte Metabolism of the National Heart, Lung, and Blood Institute to facilitate experiments to determine the transepithelial resistance of in vitro kidney tubule preparations. The determinations are made by passing electric currents through the preparation and measuring the resulting voltages at each end of the tubule. Previously, a pulse generator was used to initiate a current pulse of fixed intensity and duration, and a storage oscilloscope recorded the voltages. Measurements must be made under steady state conditions, so the investigator had to estimate the proper pulse duration to achieve the steady state. Since voltages are needed for a number of current values, the measurement procedure was tedious, time consuming, and prone to error.

The new microprocessor controller lets the user specify a series of current values of various intensities. It then applies each current in turn, determines the time at which the preparation's response has reached the steady state, records the response, and removes the stimulus. After cycling through all specified currents, it prints a table of measured voltages on a teleprinter. The complete set of measurements takes only a few moments, and can easily be repeated to verify results.

In addition to supporting research programs in other parts of NIH, CSL engineers and scientists often initiate research and development programs of general interest to the biomedical community. B/I/D programs are then served by these developments.

There has been considerable interest in CSL in applying modern software engineering principles to computer communications and network architecture. Other work centers on the investigation of applications of microprocessor technology to laboratory data acquisition and control and to the development of new biomedical and clinical instrumentation. One fine example of spin-off from this kind of work is the Distributed Laboratory Data Acquisition and Control System project in conjunction with the National Institute of Arthritis, Metabolism, and Digestive Diseases. The system consists of a network of microcomputers connected by way of a communications processor to a central data processing computer. Each remote microcomputer handles the realtime data acquisition requirements and provides instrument control functions for a single instrument or laboratory. The collected data is transmitted, at a convenient time, to the communications processor using a data communications protocol that ensures error free transmission. The communications processor serves as a store and forward front-end to the central computer. An important feature is that the user needs only minimal knowledge of the communications process. A simple command entered at the remote microcomputer is all that is required to transfer a data file. All details of the transfer are handled by the network.

Good R & D programs require good tools. For many years, CSL has had an electronics laboratory. More recently, a computer laboratory has been added. The computer laboratory facilities include "development systems"—minicomputer and microcomputer systems—that are used to investigate and implement new software and hardware for eventual use in target computer systems, i.e., systems intended for use in specific projects. These development systems let work begin on a project long before the target system ordered for that project is delivered, thus improving productivity and reducing the time until project completion. This year, the computer lab facilities were expanded so that more people can use the development systems at the same time. Virtually all minicomputer and microcomputer development work can now be done using development systems.

Development systems are indispensable to microprocessor projects since software development work is often not possible on the microprocessor hardware itself. As microprocessors become faster and more powerful, they are being used more and more as low cost substitutes for minicomputers and in situations that used to require special purpose hardware: data acquisition systems, interfaces between instruments and computers, and programmable instrument controllers. As a result, the importance of the computer lab has increased markedly.

The Laboratory is called upon for consultative assistance in its areas of expertise by both the intramural and extramural programs. Usually such assistance is limited to providing expert advice—the conventional definition of consulting. Occasionally, however, a consulting role may lead to engineering or software work, or even to a full-fledged project. Last year, CSL did a study for the NIH Library to determine the potential uses, costs, and benefits of computers for automating library functions such as circulation, cataloging, and ordering. This led, this year, to the preparation of an RFP for a library computer system. CSL involvement in the procurement and implementation of a library system is expected during the coming year.

CSL continued its support of the annual international conference, Computers in Cardiology. The conference provides a forum for direct interaction and exchange among physicians, computer scientists, and engineers who are using computers to assist research or clinical care in the field of cardiology. CSL's part in the 1980 conference is greater than in past years. Because DCRT is the host organization this year, CSL is planning and organizing the conference, to be held at Williamsburg, Virginia on October 22-24, 1980.

Future Plans/Trends

The outlook for FY81 and beyond is affected by several sets of circumstances. Economic and technical developments in large scale circuit integration are increasing the number of useful and affordable minicomputer and microcomputer applications to biomedical research. Furthermore, many of the functions CSL engineers once performed by designing special hardware are now done with microprocessors. As a result, an increasing amount of effort now goes to the development of software and firmware. To remain highly responsive to NIH's research needs in the face of continuing personnel retrenchment, contracts for software services are being established. A basic ordering mechanism for these services should be in place during FY81. Then the many well-defined software tasks that arise from month to month can be easily ordered and obtained in a timely fashion.

The manufacturers of computer hardware, by using technological advances, are able to provide far more sophisticated central processors at much lower cost/performance ratios than in the past. This new breed of computer greatly increases the scope of work that CSL can undertake. The general area of image display and processing is a good example. A few years ago, image work (because of the huge number of data points that make up even a modest picture) was limited to very large and expensive installations. Today, CSL is able to set up the tools for image analysis by employing computers that would have been completely out of reach just a short time ago. CSL engineers and scientists are in fact now planning for an image processing facility including a virtual memory computer and several high quality displays. This facility will be installed for use by scientists from throughout the NIH community whose work can be aided by image analysis techniques.

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Sharrow, S., Thomas, C., Levy, I., Powell, J., Chused, T.: Analysis of Two Color Fluorescence Using Dual Lasers. Cell Sorter and Flow Cytometry Meeting, October 21-23, 1979, Annapolis, MD.

Songco, D., Allen, S., Plexico, P., and Morford, R.: How Computers Talk to the Blind: Sightless Computer Programmers Provide Input by Keyboard and are Responded to by a Synthetic Speech Unit. *IEEE Spectrum,* May 1980, pp. 34-38.

Fiscal year 1980 was the Laboratory of Statistical and Mathematical Methodology's sixth year as a separate entity within DCRT. Looking over LSM's expanding volume of computational and consultative service are James E. Mosimann, LSM Chief, and George A. Hutchinson, Biomathematics and Computer Science Section Head.

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

Function

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer, and information science with collaboration and service in these areas to NIH researchers and administrators.

In addition to the position of the chief, the laboratory has fifteen full-time professional positions distributed among four sections:

- The **Statistical Software Section** (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large program packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.
- The **Biomathematics and Computer Science Section**(BCS), directed by a mathematician, performs independent research and provides consultation and collaboration in the specialities of its five computer and mathematical scientists.
- The **Statistical Methodology Section**(SMS) works closely with the Statistical Software Section. Three professionals in mathematical statistics provide biostatistical consultation and do independent research.
- The **Medical Information Science Section**(MIS) investigates and develops methods for application of information and computer science to medical language data processing. Two computer specialists work under the direction of a computer systems analyst who is an expert in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes, with other Federal agencies outside HHS, and with biomedical researchers worldwide. FY 80 was LSM's sixth year as a separate entity within DCRT. The volume of its computational and consultative services continued to expand; its research activities maintained about the same level as the preceding year.

A major part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When it offers a package to the NIH community, LSM makes three basic commitments:

1. Maintenance of the package, with adequate documentation, through NIH computer system changes, package updates, and corrections.
2. Rapid response to queries concerning user access to a package program, including job control language and program parameters.
3. Assistance in interpretation of results.

During this year, as in the past year, the Statistical Software Section of LSM maintained the following program packages and programs on the IBM 370 system of the DCRT Computer Center:

BMD, BMDP, Biomedical Computer Programs, UCLA

SPSS, Statistical Package for the Social Sciences, SPSS, Inc.

SAS, Statistical Analysis System, SAS Institute,Inc.

P-STAT Statistical Package, P-STAT, Inc.

IMSL, International Mathematical and Statistical Libraries, IMSL, Inc.

MSTAT1, Collection of Mathematical and Statistical Programs, DCRT

There is a major committment to maintain these packages and respond to queries about their use. During this year every package went through at least one major update. During FY 80 alone the SSS staff responded to over 4,000 calls.

The Biomathematics and Computer Science Section maintains several program packages and specialized systems on the DEC-10 system of the Computer Center. Foremost in use is the interpretive program MLAB, designed (by LSM scientists) for biomathematical modeling. Another LSM staff member has written and maintains C-LAB, a collection of programs for pattern recognition and clustering. BCS supports the PROLOG system (for non-numerical data processing) and REDUCE, an algebraic manipulation language. BCS also supports a DEC-10 version of IMSL whose S/370 version is supported by SSS. The Unified Generator Package, written and maintained by a BCS staff member, is on DCRT's System 370.

As a result of LSM's policy of not only supporting the use of these program packages but also aiding in the interpretation of their output, the statisticians of the Statistical Methodology Section provide consultation over a wide range of scientific fields. Some very brief consultations are very successful because there is a known answer to the question at hand. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

Research projects in LSM vary widely from studies of natural language processing for medical information systems and studies of efficient algorithms for information retrieval to studies in mathematics and statistical methodologies for biomedical applications.

Highlights of the Year's Activities

Computation

In FY 80 LSM put a special effort into instruction on, and documentation of, program packages. The SSS staff taught a total of eight courses on the SAS package. Extensive documentation was prepared for MLAB, which was used by several hundred NIH researchers in FY 80. A new *Beginner's Guide to MLAB* and a revised *MLAB Reference Manual (Ninth Edition)* were distributed. A series of tutorial articles on MLAB in *Interface* was begun; four articles have appeared to date. The DCRT course in MLAB was divided into two levels, beginner and advanced. MLAB was enhanced by technical improvements, which increase speed of computation and reduce memory requirements. New graphics linetypes for contour maps and a new matrix operation were added.

LSM activity was significantly affected by the increased use of statistical packages, which was almost doubled in FY 80. The average accesses per month of the SSS statistical packages alone rose from 12,000 during FY 79 to 23,000 in FY 80. Package use over the past five years is shown in Figure 1.

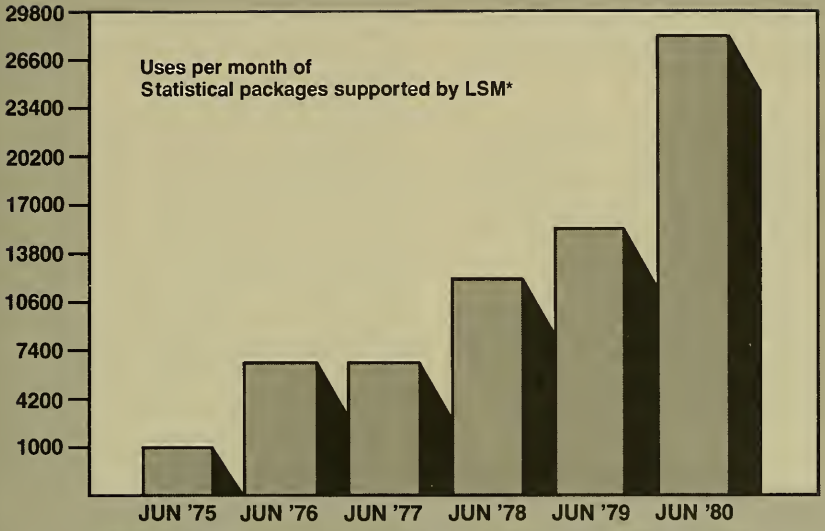
Consultation

The pattern of LSM consultation in FY 80 was similar to that of the previous year. Most consultations (55 per cent) involved statistical advice combined with considerable computer use. Others (40 per cent) involved computer use alone, and a small fraction (5 per cent) involved mathematical or statistical advice with only limited computer use. The following examples illustrate the great variety in both the nature of and the time required by LSM consultations.

For several years LSM has worked with Drs. Wineman, Hirschman, and Wolfson of NIAMDD on a study of reasons for hospitalization of patients with end stage renal disease on maintenance hemodialysis. Multiway table analyses were used. A method was devised for the analysis of hospitalization rates when patients are observed for varying lengths of time. The final paper was prepared this year.

Another collaboration, with Drs. H. Hoffman, DRS, and R. Webber, NIDR, involves research in mathematical and statistical methods, as well as in the biomedicl fields concerned. Variation in the shape of the mandibles among genetically different strains of laboratory mice is being studied to help control genetic purity of the strains. This uses symmetric axis geometry as well as multivariate size and shape analysis, both the subject of research by LSM members. Special computer programs have been prepared for this ongoing study.

A consultation with L. Geiger, DRG, required considerable effort but no new research in computer



***Packages supported by the Statistical Software Section only. Does not include packages supported by the Biomathematics and Computer Sciences Section.**

science or mathematics. The Unified Generator Package, supported by LSM, was used extensively to make inverted files or indexes from three files: the IMPAC file on NIH grants, contracts, and intramural research; the NIH Clinical Trials file; and the expertise field of the CMIS file (Committee Member Information System). The new indexes permit searches based on Boolean combinations of terms occurring in the text. Such searches are quick and of minimal cost. The Unified Generator Package created both the software for generating the indexes and the software for subsequent searches.

As an example of a long-term effort which involved statistical analysis but no new research in statistics, LSM collaborated on two studies with A. Tahmoush, NINCDS. The first study of physiological measurements in patients with Causalgia (a pain syndrome), employed both multivariable parametric and nonparametric methods, as well as extensive computations and data reduction. The second study involved one of the instruments used in studying

Causalgia. This instrument uses backscattered light to permit noninvasive measurements of blood flowing through an artery. An in vitro system is being used to study effects of changing pressure and flow in the instrument's readings. This study also involves several variables and considerable computer analysis using SAS, BMDP, and SPSS.

A typical statistical consultation that involved intensive effort over a short period of time took place with M. Daniel, NHLBI, studying synapses in chick retinas. It required knowledge of small sample properties of the Kolmogoroff-Smirnov statistic, a nonparametric statistic for testing differences in two populations. Intensive effort over a single week developed the needed probabilities, which were computed using only small modifications of SPSS output. In this case the nonparametric tests gave results consistent with a prior biological hypothesis.

Research

This year research in the BCS included projects in computer science, biomathematics, and general mathematical methods. In computer science, studies of logical and heuristical methods continued for non-numerical data processing using the PROLOG and REDUCE computer languages. A computer classification of medical words pertaining to inflammation and and certain surgical procedures was completed. A computer algorithm capable of making syllogistic deductions from pairs of English sentences was constructed; algorithms for interpretation of paragraphs of straightforward technical information are under study.

In biomathematics, BCS research continued on the "symmetric axis" method for describing biological shapes and their growth and development. Symmetric axis methods for analysis of three-dimensional data, such as for data generated by scanners, were developed. Currently, methods for symmetric axis analysis of gray-scale data, as well as for spherical data (such as observed during embryonic growth) are under development. A collaborative study of human mandible development was completed and is being extended to other primates.

A collaborative project involving analysis of enzyme data from the blood serum of normal subjects and cancer patients was completed. The BCS investigator developed a method of transforming the data into multivariate data points suitable for cluster analysis using C-LAB.

In SMS, research on simultaneous statistical inference was continued. New results were obtained on ratios of means in multivariate normal populations where the several populations need not have the same covariance structure.

Through contract with the Biometrics Unit at Cornell University, SMS is supporting study of the interpretation and utility of the output of variance component routines in a variety of current statistical package programs. Performance of the programs with unbalanced data is under study.

In the Medical Information Science Section, collaboration was renewed with the NCI Laboratory of Pathology, which plans to encode its entire corpus of surgical pathology diagnoses since 1953. Lexical studies and revisions, both for retrieval accuracy and linguistic completeness, were accomplished in collaboration with Dr. D. Henson of NCI. MIS participated in the design of a data base for the Laboratory of Pathology which will become part of the DCRT Clinical Information Utility, a research data base tool for the NIH Clinical Center.

In addition MIS constructed a stem dictionary for the "viral hepatitis" knowledge base produced by the National Library of Medicine. Also, work was done on automated morphosemantic analysis and paraphrasing of medical terms derived from Greek and Latin. In addition, an experimental comparative study was made of medical compounds in English, French, Italian, Spanish, and German.

Future Plans

No major shift in laboratory service or research is anticipated in the coming year. Current levels of statistical and mathmatical program packages support, consultation, and user assistance will be maintained. Research projects will be continuations of those already initiated and reported here.

Publications

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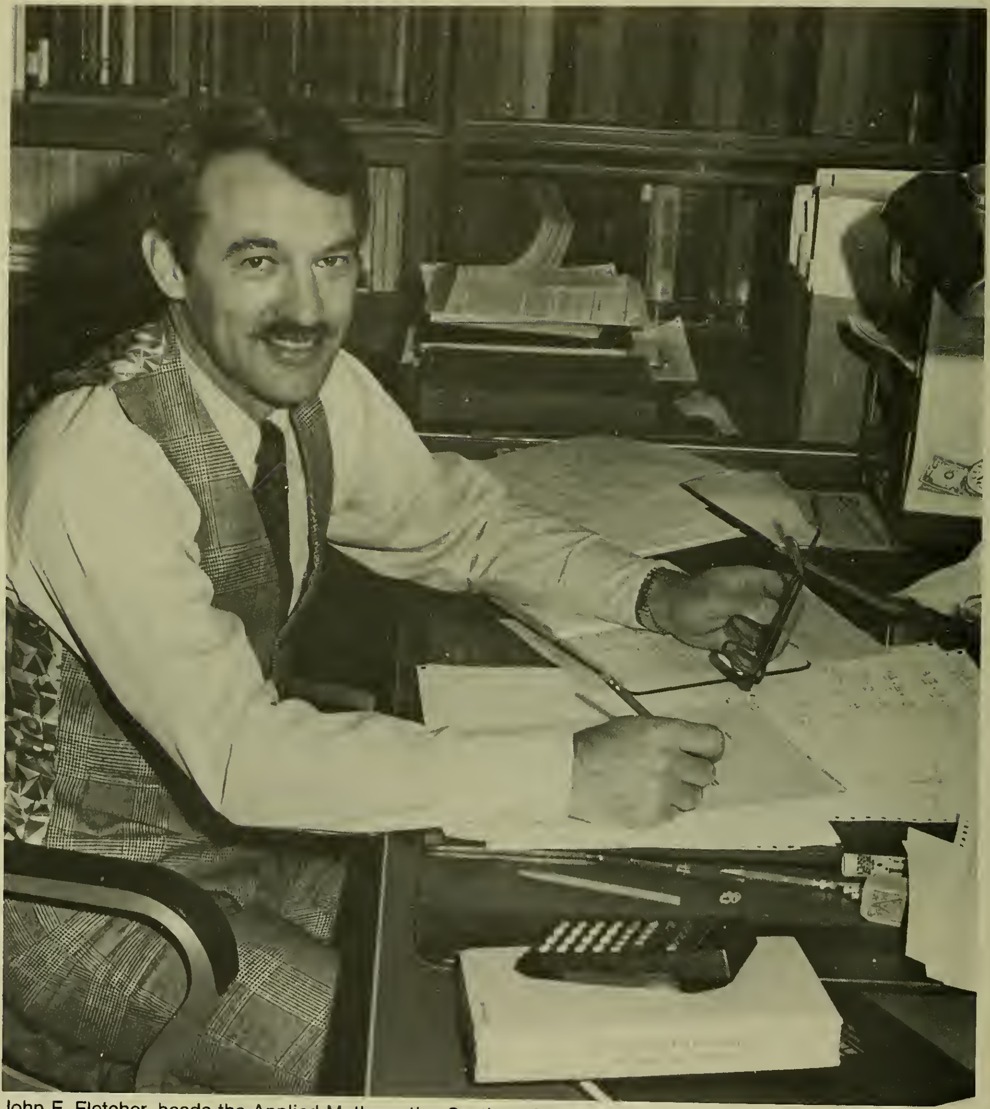

John E. Fletcher, heads the Applied Mathematics Section of the Laboratory of Applied Studies. He is also the Chairman of the Mathematics Department, Foundation for Advanced Education in the Sciences.

Laboratory of Applied Studies

Eugene K. Harris, Chief

Functions

The Laboratory of Applied Studies (LAS) has three main purposes:

1. in collaboration with biomedical scientists, to apply mathematical theory and computing science to the construction, testing, and improvement of mathematical models of physiological processes—particularly reaction-diffusion processes, transport of substrate to tissues, and models of receptor-ligand binding kinetics;
2. in collaboration with clinicians, to develop and apply mathematical or statistical theory and computer programming to improve diagnosis of disease and assessment of treatment;
3. to engage in independent research in applied mathematics, statistics, and computer systems necessary to provide a sound theoretical basis for collaborative studies, and to insure that state-of-the-art mathematical and computational methods are available as research tools at the NIH.

Two sections carry out these primary LAS functions:

Applied Mathematics Section (John E. Fletcher, Ph.D., Chief). This staff of six includes specialists in applied mathematics, computer science, biomathematics, and medicine.

Medical Applications Section (James J. Bailey, M.D., Chief). This six-member staff includes physician-scientists, electronics engineers, and computer systems analysts.

The Chief, LAS, is a biostatistician.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. Largely, these involve collaboration with other groups at NIH, elsewhere in the U.S.A., and abroad. The collaborating investigators this year included:

- *biochemists and pharmacologists* - at the University of Iowa, Medical College of Virginia, and other universities in the U.S.A. and in France—working on models for receptors of drugs or other ligands and on the kinetics of enzymes in membranes
- *physiologists and chemical engineers*—in the U.S.A, United Kingdom, Scandinavia, and Germany—studying the transport of substrate within the microcirculation
- *clinicians*—at NIH—in the cardiology, pulmonary, and hematology branches of the NHLBI; in the arthritis and rheumatism branch of the NIAMDD; and in the medical intensive care unit and the departments of diagnostic radiology and diagnostic imaging of the Clinical Center
- *clinical chemists and pathologists*—at NIH (Clinical Pathology Department, Clinical Center) and elsewhere in the U.S.A., in Europe, and in Japan—engaged in the collection and study of reference values in laboratory medicine
- *electrocardiologists and biomedical engineers*—in the U.S.A., Canada, and Europe—concerned with improved algorithms for computer-based interpretation of ECG's.

During FY80 LAS staff members participated in various teaching and consulting, or advisory, activities. J. Fletcher continues to serve as Chairman of the Mathematics Department, Foundation for Advanced Education in the Sciences.

J. Bailey continues as a member of an NHLBI site-visiting team concerned with computer analysis of exercise ECG's. He also serves as consultant on common standards for quantitative electrocardiography for an EEC-sponsored program in medical and public health.

E. Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris also serves as consultant statistician to the College of American Pathologists and to the International Federation of Clinical Chemistry (Expert Panel on the Theory of Reference Values), and is a member of the Board of Editors of *Clinical Chemistry*.

Highlights of Year's Activities

Major accomplishments during this year are in the highly technical areas of developing and implementing various computer systems for support of LAS collaborative research projects. Some examples are:

- An interactive software package called PICTUR has been developed by M. Douglas of the Medical Applications Section for use on the DeAnza image processing system. It offers the user many options for analysis of scintillation, ultrasound, and electron-microscopy images, in color and grey levels.
- A computational tool called SPICE (Simulation Program for Integrated Circuit Electronics) has been implemented on the NIH DEC-10 system by B. Bunow of the Applied Mathematics Section, to provide a means of simulating a network of thermodynamic changes. When coupled with another computing system (NET-2) now being installed by Dr. Bunow, a powerful support system will be available to simulate and study the flow of reactive materials through membranes and within cells.
- A set of programs for the NIH 370 computer system has been developed by M. Horton (Medical Applications Section), G. Shakarji (DMB), and D. VanSant (LSM) for study of simulated and real clinical laboratory data using multivariate time series models. These programs will permit research on the sensitivity and specificity of such models in detecting sudden changes or trends in clinical measurements of patients under long-term monitoring.
- The use of the LAS MAC-16 computing system has been greatly facilitated by E. Pottala and A. Mitz (Medical Applications Section). They developed and installed an operating system which provides easy access to compilers and major programs and automatically allocates system resources during execution of user programs.

Future Plans

The promising studies in computer-based pulmonary pathophysiology, initiated by Dr. T. Stibolt (who has left to complete his residency in internal medicine after 3 years of excellent, devoted work in LAS) will be continued by his successor, Dr. R. Burgess. Within time and personnel constraints, it is planned that the application of scintigraphic techniques to the diagnosis and monitoring of renal hypertension will also proceed through additional studies in dogs to eventual use in patients.

Continued progress is expected in all other active projects as well, including:

— development of specialized mathematical methods for representing the microcirculation of perfused organs,

—application of the DeAnza image processing system and other computing systems to cooperative studies with Institute/Division scientists interested in the distribution of various proteins and inorganic ions within cells,

—further development of mathematical methods and numerical algorithms for the solution of partial differential and other nonlinear equations, and

—comparative study of multivariate and univariate models in the analysis of biochemical time series.

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In his work with laser light scattering, PSL Physicist Ralph Nossal performs studies in order to understand how laser Doppler techniques can be used to measure capillary blood flow in tissues.

Physical Sciences Laboratory

George H. Weiss, Chief

Function

The Physical Sciences Laboratory has three principal functions:

- *to carry out research* in the physical sciences in order to understand biological phenomena in terms of physics and chemistry
- *to develop theory and practical instrumentation* for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology
- *to provide consulting services* to other scientists at NIH in physics, theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of six professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes, and problems in applied mathematics.

Scope of Work

The Physical Sciences Laboratory has a combined program of research projects internal to the laboratory and collaborative projects with scientists at NIH and at other institutions. The collaborative projects, done jointly with approximately twenty five other investigators, include two major projects with data being generated by off-campus scientists.

Highlights of the Year's Activities

Although the PSL has devoted most of its past efforts to research in the physical sciences relevant to NIH's mission, this year has seen a contribution that could speed the publication of articles in scientific journals and lead to considerable financial savings to NIH and to other research establishments. Dr. Adrian Parsegian has shown that it is feasible to interface most word processing machines with a typesetting computer—allowing, in effect, an author to typeset his own article. The advantages of this system are that it minimizes typesetting errors and reduces printing costs considerably because much of the printer's labor is eliminated. Preliminary tests of this method have been made on articles for the *Biophysical Journal* and for a book published for a meeting on proteins and nucleoproteins. The results of this experience indicate that a savings in cost of at least 50 percent is possible. Programming is in progress to create the software needed as an interface between word processors and other typesetting computers.

A new 360 MHz NMR spectrometer was purchased and installed in a cooperative project with NHLBI and NIMH. Dr. James Ferretti has spent a considerable amount of time in helping to overcome troubles in the new instrument. Preliminary experiments with the spectrometer indicate that two-dimensional Fourier transform spectroscopy is feasible, allowing a considerable enhancement in resolution of fine structure. This possibility has allowed Dr. Ferretti to resolve resonances in the protein spectrum of bleomycin that have never been resolved with other methods and instrumentation. Further research on the conformation of bleomycin and its interaction with Fe-57 is in progress.

Dr. Nossal has developed a theory for the diffusion of laser light in tissue microvasculature. The theory allows one to relate changes in the spectrum of scattered light to changes in blood volume. The theory has been verified by measurements of particle flow through model tissues by Dr. R. Bonner, BEIB. Such a theory is necessary for the development of a laser Doppler instrument to measure peripheral blood flow.

Dr. Parsegian has continued his investigation into the nature and measurement of intermolecular forces in phospholipid bilayer membranes with the collaboration of Professor R. P. Rand of Brock University. They have been systematically determining the forces operating at distances of 30 Angstroms or less and have shown that the dominant force between membranes that are stable in water is due to the work of removing water between the approaching surfaces. Electrostatic interactions between charged bilayers with adsorbed ions have also been measured, leading to a possible understanding of the activity of enzymes that modify these groups and reside on the bilayer surfaces of naturally occurring residues. The techniques developed by Drs. Parsegian and Rand are now also being applied to the measurement of protein interactions.

Future Plans

All of the projects just mentioned are in progress and will continue into the following year and beyond.

The typesetting project will be extended by creating software interfaces between WYLBUR files and printers' typesetting computers for journals that are popular with NIH authors, and by negotiating with journal publishers for the implementation of these techniques.

NMR investigations on the conformation of angiotensin, bleomycin, and bradykinin will be extended. Future measurements on bleomycin will be undertaken to assign those nitrogen atoms in the bleomycin complex that are ligated to iron molecules. This investigation is expected to shed light on the mechanism of action of bleomycin.

The laser light scattering project will be extended to develop further clinical applications of related optical techniques.

A collaborative project on quantitative aspects of audiometry will probably receive more attention in the coming year. A start was made on this project last year, by manually digitizing a large number of tympanograms. However, digitization done this way was unreliable. This year instrumentation was ordered so that the tympanograms could be produced directly in digital form. When this instrumentation is in place, a study will begin to establish baseline values on normals for parameters of interest.

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The Office of the Director complements the work of the six laboratories and branches of DCRT. Key staff members include (left to right): L. Lee Manuel, Executive Officer; Frances F. Sarles, Secretary to the Director; Dr. Arnold W. Pratt, Director; Dr. William C. Mohler, Associate Director; and Henry J. Juenemann, Assistant Director.

The three DCRT Offices complement the work of the six Laboratories and Branches by:

- coordinating the complex Federal policies and procedures that govern getting and using computers at NIH.
- providing general administrative management support for the Division's work.
- serving as a central source of information about the DCRT activities and about computer related disciplines.

Office of ADP Policy Coordination

Henry J. Juenemann, Chief

Functions

The Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has two closely related functions.

1. It serves as a focus for NIH-wide coordination of automatic data processing policy matters.

2. It serves as a central NIH point of contact with the Public Health Service, the Department of Health and Human Services, other HHS Agencies, The General Service Administration, and the Office of Management and Budget on policy questions and NIH's participation in policy development.

The Office also provides advice and assistance concerning internal DCRT operations and coordinates DCRT's ADP policies and activities with those of other agencies.

Scope

The role of the office includes: advising the Director of DCRT and through him the Director of NIH on ADP policy matters; assisting the NIH Division of Management Policy on questions relating to its responsibility for administrative and management computer applications; reviewing and evaluating proposals from NIH B/I/D's for ADP and computing related procurements and contracts; directing the development of the annual NIH ADP Plan; representing the NIH in PHS and DHHS policy formulation efforts; working with GSA staff on procurements; coordinating Interagency Agreements with other Federal agencies that use DCRT facilities; and answering inquiries from scientists and administrators who are confused by the whole process.

Highlights of FY80 Activities

During the year this office reviewed nearly 500 proposals for procurement of ADP equipment and/or services in order to ensure that each was justified and in conformance with PHS, HHS, GSA, and OMB guidelines. In some cases suggestions were provided to the NIH Procurement Branch as to the most expeditious procurement route to follow. In many cases one or more of the Laboratories and Branches of DCRT provided expertise to help this office review technical aspects of the proposals.

A major highlight of the year was the complex reprocurement of the whole of the NIH general purpose central computing system. During the fifth year of this process a final competitive solicitation package was issued in January. Approximately 400 written questions were received from four potential vendors and were answered in writing with appropriate amendments to the solicitation package.

On the last day before proposals were due, a protest was filed. Dealing with the protest was a major effort for the remainder of the year.

Because of the protracted nature of the total reprocurement and the continued growth in user demands placed on the NIH Computer Center, it became necessary to ask for a temporary interim capacity upgrade pending completion of the total reprocurement. This action required NIH, PHS, HHS, and GSA approvals. The action was initiated on January 8 and sucessfully completed on June 20. Thirty-six individuals outside of DCRT had to approve of, or concur in, various aspects of the action—some, on several aspects.

Arrangements were completed by this office to reassign the computer system replaced by this interim upgrade. It went to the National Library of Medicine. At the time of this writing arrangements were also being made for the 158 MP displaced from NLM to be reassigned to provide improvement to the processing power on which the Clinical Center's Medical Information System depends. Assistance was also provided to the Clinical Center to obtain approval for an extension of the present contract for the Hospital Information System and in preparing for a total reprocurement of that system.

In addition, total reprocurement of the DCRT Scientific Time Sharing system moved from the stage of a draft solicitation to a completed award.

This office provided assistance to the Division of Research Resources to develop an approach to upgrading the PROPHET System, the Chemical and Biological computing resource which serves NIH's grantee community. Assistance was provided to the Gerontology Research Center of the National Institute on Aging to develop specifications and later conduct a procurement for one system to serve as a data collection, data processing, and remote access interconnection with DCRT computers and for another system to replace the aging Raytheon 706 computer. Both were successfully completed as was a procurement for a major share of the equipment necessary for a new image processing system within DCRT.

As the year closed a major project to automate the NIH library was under way. This was a joint project by the Computer Systems Laboratory and Division Research Service staffs with assistance from this office for policy, clearance, and procurement aspects. Along the way the office carried out its usual annual assortment of other tasks including coordination and preparation of the Annual NIH ADP plan. This document combines projections of all NIH Bureaus, Institutes, Divisions, and Offices for ADP expenditures over the next four years as part of the NIH budget submission required by the Department and the Federal Office of Management and Budget.

Future Plans

Federal ADP policies and requirements continue to become more and more complex as OMB, GSA, DHHS, and PHS become more and more involved. As a result, the Office must spend an increasing portion of its available man-hours in attempting to guide NIH policy in productive directions and in meeting regulatory requirements. The Office will continue its work to spare large numbers of NIH research and research support staff members the task of becoming expert in the many nuances of ADP-related regulations.

Office of Administrative Management

L. Lee Manuel, Chief

Function

The Office of Administrative Management, under the direction of the Executive Officer, provides administrative, financial, and personnel management in support of the Division's programs. The office serves as liaison between these functions and the NIH Office of Administration, Office of Research Services and with other NIH, PHS, and DHHS offices.

Scope and Activities

The office handles a broad range of administrative managerial functions for an NIH research division of almost 300 people. The Financial Management/Project Control Sections maintain 2000 project accounts involving 7200 registered users of the DCRT computer facilities and services; these services totalled an estimated $24,000,000 in FY 80. The Administrative Services Section processes requisitions, contracts, travel, and training documents; this variety of procurements totalled approximately $20,000,000 in FY80. Day-to-day activities also include managing personnel space, telephone charges, payroll, and other miscellaneous administrative subjects.

Highlights of FY80 Activities

The Personnel Section completed its mandated three year position classification review of all DCRT positions. It implemented the senior executive service and merit pay system at the DCRT. Evaluation criteria were implemented to cover appraisal of supervisors and managers at the GS-13 through GS-15 level for 31 merit pay employees.

The Financial Management Section was the primary focus for development and coordination of information for the DCRT portion of the NIH Forward Plan, Zero Based Budgetary Workload/Manpower reporting, and the standard Federal Budget process.

Additional new requirements from the DHHS Secretary required intensive efforts by the Administrative staff in the areas of contracting, procurement, travel, and consultant services. Most of these requirements called for detailed plans to be prepared, mandated monthly and quarterly reporting requirements, and elevated certain delegations of authority to higher levels. All of these actions tended to increase the amount of "paperwork" required and further slowed the already cumbersome administrative processes. The DCRT Administrative Information Retrieval System (AIRS) was used to generate staffing charts this year from the plotting facility. This eliminated a lengthy typing chore for the staff and significantly reduced the cost of preparing these charts.

The Department conducted a systems security audit of the central facility and the Project Accounting System program. Preliminary comments show a few violations of a minor nature and the draft report has been received and commented on.

Future Plans

The major renovations of Building l2 and l2A will be completed in the coming year. These renovations will conclude the long-range plans developed several years ago and will allow for adequate physical security in the central computer complex. As further guidance on the new DHHS EEO program is received, new monitoring systems may have to be initiated to evaluate DCRT performance in this area. There undoubtedly will be new administrative managerial requirements and modifications of old ones forthcoming from the NIH, the PHS, the Department, the GSA, and the Civil Service Commission.

Office of Scientific and Technical Communications

William C. Mohler, M.D., Chief

Functions

The DCRT Office of Scientific and Technical Communications (OSTC), under the direction of the Associate Director, DCRT, includes:

- The DCRT **Library,** which maintains a collection in computer science and mathematics, statistics, engineering, information science, and management.
- The DCRT **Information Office,** which serves as the focus for providing the NIH community and the general public with information about DCRT's activities and their relationship to biomedical research.
- **Scientists** assigned to this office, working in related areas of pattern recognition, multidimensional information processing, and medical information science.

Scope of Activities

The DCRT Library is a small, independent, special library, staffed by the Librarian and a library technician. It performs the full range of library activities and has access to a wide variety of online information services and data bases. Its collection of monographs, periodicals, and other documents covers subjects related to the work of DCRT.

The Library supports the work of the DCRT staff and serves as a resource for employees in the rest of NIH. It is an integral part of the Washington area network of special libraries and cooperates with libraries outside the area to share resources. It does this through organizations such as the Interlibrary Users Association of the Washington Baltimore Area, The Metropolitan Washington Library Council, FEDLINK (a Federal library consortium) and at the national level, the OCLC network.

The DCRT Information Office, too, is small and handles the full range of activities of an NIH Information Office. The Information Officer, assisted by a Public Information Specialist, answers inquires, produces and distributes print and audiovisual materials, and arranges briefings and tours for visitors. They coordinate special events, work with members of the media and provide advice, assistance, and educational resources on communications for the DCRT staff. The office is responsible for all Freedom of Information requests coming to DCRT.

A significant part of the Information Office program is directed toward improving within the NIH understanding of the Division's work and the application of computing to biomedical research. But the scope of its communications includes Federal agencies, schools, libraries, private industry, medical organizations, and a wide variety of individual scientists and lay persons. The staff of the office is active in the NIH information community and Washington area associations of communication professionals.

The other professional activities of OSTC derive from the interests of its scientific professionals: a mathematician, a computer scientist, an information scientist, and a physician. They work with other professionals at NIH and with a wide variety of medical and technical groups, government and private, outside of NIH. They have research and development projects on biomedical data bases, image processing, and decision analysis.

Highlights of FY80

The DCRT Library completed development and installation of its automated circulation system. New report programs, written by the DCRT Data Management Branch, give a better overview of activity among books and borrowers. A new set of indices for the document collection now provides access by author and keywords in the document titles.

The Librarian worked with the DCRT Computer Systems Laboratory as consultant to the NIH Library to develop specifications for procurement of a new computer based system for its operations. She and the Chief of the Data Management Branch helped scientists from NIAMDD and NHLBI explore the options for acquiring their own computer based system for maintaining and searching files of citations to articles in the biomedical literature. She served as the Chairperson of the delegation from FEDLINK (the Federal Library Network) to the Users Council of OCLC, INC., a national cooperative library network.

The Library and the Division lost a valuable member when Ms. Jill Lindau accepted a position as a librarian at the Library of the Bureau of the Census. She began as a clerk in the DCRT Library, in the early 1970s, advanced to library technician and received her M.L.S. degree in 1979.

The Information Office made substantial progress on its program to complete a basic set of information documents about all DCRT activities. The effort to develop better ways to present this information included a major revision in the format of the Annual Report. New courses in Effective Technical Writing were added to the program begun by the office last year to help DCRT staff improve their communication skills.

The stream of requests and inquiries coming into the Information Office increased about 50 per cent this year. The audience for DCRT publications also increased, to a total of 4,800 items this year. Visitors getting briefings and tours ranged from a Montgomery County Girl Scout Troop to scientists from Australia, China, and the Soviet Union.

There were two dozen Freedom of Information requests, most from individuals connected with private computer organizations. A great deal of time went into handling this with administrative cost to the government over $1,500. DCRT sent the Department several suggestions to modify regulations to help recover some of these costs.

The Information Officer worked with DCRT scientists on a project to develop techniques for computer based preparation, editing, and typesetting of articles submitted to scientific journals. She served on the NIH Information Officers Training Committee, was active in the National Association of Government Communicators, and was elected president of the Washington chapter of Women in Communications, Inc., a national organization for public relations, journalism, broadcasting, and communications professionals.

Dr. Judith M. S. Prewitt continued her collaboration with Dr. B. R. Hunt at the University of Arizona in a study group sponsored by the Office of Naval Research and the National Science Foundation to formulate the automation of image processing. She developed a new collaboration with Dr. K. S. Fu, Purdue University, on Pattern Recognition and Image Processing and on Parallel Algorithms and Computer Architecture. As principle investigator, she began a project sponsored by the Goddard Space Flight Center, NASA, to evaluate the utility of the NASA/ Goddard Massively Parallel Processor for biomedical applications.

The scope of Dr. Prewitt's other work is indicated by the publications listed at the end of this section. Dr. Sanjay Ranade joined her during the last half of the year as an NIH Staff Fellow to develop and apply algorithms for the processing of cellular and tissue images, including a new project on the analysis of muscle in collaboration with Dr. Robert Burke, NINCDS.

Mr. Martin Epstein provided technical advice and counsel to the Lister Hill Center, NLM, for its medical knowledge base program, and in the Spring he accepted an appointment as Assistant to the Director of the Center. He finished his doctoral dissertation for the University of California, San Francisco, on Natural Language Access to Clinical Data Bases. His MEDINQUIRY system is the cornerstone of a collaborative project with investigators at UCSF, The University of Pennsylvania, and SRI International to develop and use enlarged data bases covering patients with malignant melanoma.

The Computers in Clinical Medicine course for medical students was again organized by Dr. William C. Mohler, under the NIH Clinical Elective Program. Dr. Mohler continued to work with the NIH Clinical Center to apply the DCRT Clinical Information Utility to patient care and clinical research.

Plans

Plans for the coming year will follow the lines set in FY80 and previous years.

The Library will try to cope with two changes that have formidable consequences for all libraries: A new edition of the *Anglo American Cataloging Rules* (AACR2) will be implemented in 1981 and the Library of Congress will shift to an online catalog. Some form of automated catalog system will be necessary for libraries to keep up with these changes. At NIH, the DCRT and the NIEHS libraries are too small to initiate separate efforts to develop this kind of system. The DCRT and NIEHS librarians have met with the NIH Library staff to explore a cooperative effort based on the NIH Library contracts for library automation systems.

The Information Office will continue to develop and improve materials to tell people what DCRT does and how computers are used in biomedical research. This will include some new audiovisual packages for use at NIH and perhaps for export in response to requests from outside NIH. The Information Office will survey both the DCRT and the NIH to bring up to date the list of needs for communications about computers at NIH.

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Division
of
Computer
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Fiscal
Year
1980

Annual Report

Volume 2

DCRT

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Oct. 1, 1979
through
Sept. 30, 1980

Projects
and
Activities

Annual
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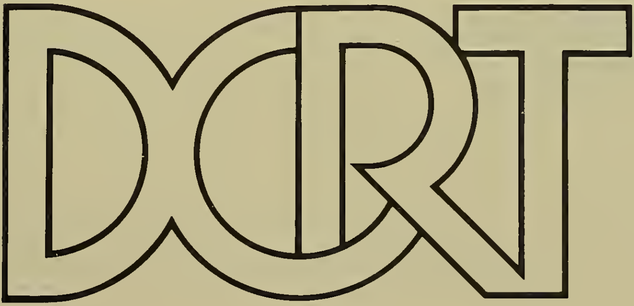
Volume II



Foreword

The work of the Division of Computer Research and Technology covers a large spectrum of activities. It ranges from doing research in biology, statistics, mathematics and computer science to providing computer facilities and services for the NIH.

The several parts of DCRT embody and integrate this variety of talents. Each part has a major functional focus. But the success of the Division's work arises from the interaction of the members of each group with others across organizational and disciplinary lines. Many projects in the Division require the expertise of people from several segments of the spectrum.

DCRT's collaboration links our staff to professionals inside NIH and also outside NIH. The result is a balance in emphasis to provide the work done by DCRT at NIH with the benefits of collaborations outside of NIH. While DCRT does not have money for grants, it does provide occasional support for meetings on scientific topics related to its work.

This year our story starts with the service end of the spectrum and moves to the research end, presented in two volumes:

Volume I gives a summary overview of the work of each group and highlights its accomplishments.

Volume II includes detailed projects and activities of each group.

If you have comments on the report or suggestions for improving future versions, please send them to:

DCRT Information Office
NIH Building 12A, Room 3027
9000 Rockville Pike
Bethesda, Maryland 20205

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Activities, Services, and Facilities
FY 1980
Computer Center Branch

Joseph D. Naughton, Chief

DECSYSTEM-10 IMPROVEMENTS

PROLOG, a simple yet powerful language, was made available on the DECsystem-10. Developed as a practical tool for programming in mathematical logic, PROLOG is an efficient alternative to LISP and other languages for applications involving symbolic data processing. Its use has been documented for such diverse applications as computational linguistics, prediction of drug interactions, automatic programming, solution of mechanics problems, symbolic integration, and architectural design.

The system default file protection code was changed to allow improved file security. The new code prevents users from reading files other than their own. The new default permits all operations by the file owner and allows other members of the same project to read but not change the file. Access is denied to all other computer users.

A new SAIL compiler and runtime system became available on the DECsystem-10, adding double precision floating point arithmetic to the SAIL language. This enhancement benefited programmers and scientists with mathematical applications that require higher precision.

SYSTEM 370 IMPROVEMENTS

Remote Job Entry (RJE) security was enhanced with the assignment of passwords for use with all RJE terminals communicating with the IBM System 370 facility. This step was taken to provide protection for sensitive information stored and/or processed on the NIH Computer Utility, as required by the Privacy Act of 1974. The password will be required as part of the sign-on procedure to ensure that only RJE terminals authorized to use the system can sign on.

TELECOMMUNICATIONS IMPROVEMENTS

The mechanical NIH Dataswitch was retired on December 1, 1979 and a new electronic Centrex switch was installed to handle all Dataphone calls to the NIH Computer Utility. The new Centrex system, which required a sizable addition to the C&P Telephone electronic switching system in Bethesda, provides the Computer Utility with more reliable service and less troublesome connections for data traffic.

RATE CHANGES

Following an uninterrupted 14 year tradition of providing the finest service at the most economical cost, the Computer Center announced rate reductions twice during the year. Processing charges for all classes of batch work executed on the System 370 dropped dramatically this year, falling from $.80 per machine unit to only $.50 per machine unit. WYLBUR users received a reduction of over 16% as the charge for editing time dropped to $.70 per second. TSO users enjoyed a 33% price reduction to $.55 per CPU second.

The cost of online (disk) data storage space fell for the first time since the installation of the online storage facilities. Storage costs were cut by 25%

from $.02 per track day to $.015 per track day. This has resulted in significant savings to holders of the 200,000 data sets currently stored online. An 8% rate reduction was offered on the DECsystem-10 making the new rate $1.15 per machine unit. The 50% deferred processing discount continued in effect for all services on both the IBM System 370 and the DECsystem-10 for work processed after 6 p.m. weekdays and all day on weekends and holidays.

Due to increasing labor costs, the Data Conversion Services saw a modest 5.25% increase to $10 per hour. Plotting services experienced a 20% increase to $30 per hour. However, even in these times of rampant inflation, the Computer Utility continued to be increasingly cost effective. The Center has plans underway which should permit continued response to users' demands for additional functions and services at even more cost effective rates.

USER TRAINING AND ASSISTANCE

New courses offered in the 1980-81 program included two new language courses for the DECsystem-10, BASIC and PASCAL. Courses were also available on several application programs such as MLAB and CLAB and on the use of the system. Users of the IBM 370 were offered courses in the use of various compilers, in Job Control Language, and in a large selection of application programs such as SAS, MARK IV, and RMAG22. Self-study courses were reorganized and greatly expanded this year and included programmed instruction and workbook courses as well as audiovisual and computer-assisted courses. Applications for training received during the year number 2,388, but only 1,618 of these could be accepted. There were 71 sessions of 37 different courses given during the year.

Programming Trouble Reports researched and answered during the year numbered 1,922. User Services applied over 1,000 system fixes during the year and installed 120 new releases of current software packages. There were 27,830 calls or visits for assistance during the year.

RESEARCH AND DEVELOPMENT

The molecular graphics system was used to develop a package of images for the teaching of macromolecular structure in universities and medical schools. Rapid dissemination of the package to 500 departments of biochemistry has resulted in a heightened interest in computer graphics as a tool for the representation of macromolecular structure.

Center researchers have also developed modeling techniques to permit the extension of crystallographically determined proteins to related proteins and have used the display system to model structures of a variety of myoglobins, insulins, immunoglobulins, and several of the proteins in the clotting cascade. Very speculative experiments have been performed to find models for calmolulin and interferon.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00046-02 CCB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Dissemination of Macromolecular Surface Representations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist
Others: None

COOPERATING UNITS (if any)

David R. Bing, Center for Blood Research, Boston, Mass.

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg. 12A, Room 3009, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords) A complete package for the teaching of macromolecular structure in biochemistry courses in both universities and medical schools was developed and disseminated to 500 departments of biochemistry The subject matter covers the different levels of macromolecular structure (peptide bond, alpha helix, beta structure, tertiary structure, quaternary structure, prosthetic groups, and active sites). The classroom teaching component consists of 116 stereo pairs which can be projected in stereo using commonly available slide projectors. The student component consists of an inexpensive cardboard viewer and seven cards which each contain seven stereo images. Manuals for both the teacher and the student help to interpret these space filling images of macromolecules. The dissemination procedure attempted to maximize geography (states in the USA and foreign countries), level (first to third level universities and colleges), and function (departments of biochemistry and chemistry in universities and medical schools). Arrangements have been made to make the complete package available from a commercial source. Additional sets of stereo slides and cards are now in preparation for inclusion in various meeting proceedings.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00036-04 CCB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Determination of Macromolecular Structure by Computer Modeling

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Richard J. Feldmann, CCB, DCRT, Computer Specialist
Others: Michael Potter, NCI, LCBGY
Bruce Furie, New England Medical Center, Tufts University, Boston, Mass.
David R. Bing, Center for Blood Research, Boston, Mass.

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg. 12A, Room 3009, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:

CHECK APPROPRIATE BOX(ES)

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The molecular graphics system has been used to determine models for the structure of a number of biologically important macromolecules. The modeling starts with the high resolution structure of one protein determined by crystallographic techniques. The amino acid side chains of a related protein are graphically substituted where they differ. Additions and/or deletions in the polypeptide chain are made and modeling is done to make the chain contiguous and stereochemically correct.

The technique has been applied to immunoglobulins, myoglobins, insulins, thrombin, factor IXa, factor Xa, calmodulin and interferon. Success with the technique varies with the degree of similarity between the starting and modeled structures. Space filling images in color and stereo made on the molecular display system of the modeled structures provides a departure point for thinking and biochemical experimentation.

Projects and Activities FY 1980 Data Management Branch

J. Emmett Ward, Chief

CLINICAL RESEARCH, PATIENT CARE, EPIDEMIOLOGY

Clinical Information Utility (CIU)

Clinical Support Section (DMB). This ongoing, major effort maintains a data base for research and patient care in the NIH Clinical Center. Several improvements were made to the CIU system this fiscal year: the data base was expanded to include vital signs data; a reporting system was developed that prints chemistry and hematology data in a matrix format; an innovative report format was developed for displaying the vital signs data numerically and graphically; a system was developed to produce the cumulative laboratory results weekly; all the preprocessor and update programs were developed for blood bank, radiology, nuclear medicine, and medication data; and surgical pathology history data are being processed for inclusion into the CIU data base.

Operation Bon Appetit/'Foods for Health'

D. Feskanich (DMB/SAS); J. Pinsky (NHLBI). This project is a continuing analysis of food sale data collected by Giant Foods in response to a "Foods for Health" campaign. Thus far, analysis indicates that if the campaign has had any effect on people's consumption habits, the changes are too subtle to detect.

Survival System

C. Creede (DMB/SAS); A. Asire (NCI). This is a life table analysis system originally developed in the 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is now the primary goal. During FY80 the system was sent to the University of Cincinnati Medical Center, the Howard University Cancer Research Center, the Cleveland Clinic, the University of Southern California School of Medicine in Los Angeles, and the Cornell Medical Center.

Kidney Transplant Histocompatibility Study

C. Creede (DMB/SAS); H. Krakauer (NIAID). This study was mandated by the KTHS Data Analysis Protocol. During FY80 Ms. Creede completed the analysis by means of frequency tables and actuarial life table analysis. The programs satisfying the KTHS protocol requests were also made available to the Harvard School of Public Health.

Combined Cardiology/Heart Surgery Data System

Larry Martin (DMB/ASPS); Roger Dailey (DMB/DBAS); C. McIntosh (NHLBI); D. Rosing (NHLBI). This combined system provides a chronological record of the medical activity of NHLBI Cardiology and Heart Surgery Branch patients. In FY80 effort was directed toward meeting the routine and ad hoc reporting requirements and statistical needs of the NHLBI physicians and researchers and toward expanding the system to include nuclear angiogram information.

NIAMDD Study of the Incidence and Prevalence of Kidney and Urinary Tract Diseases in the Armed Forces

Darius Georg (DMB/ASPS); N. Cummings (NIAID). This study is being conducted to evaluate the research needs in this area and to correlate the research needs with the occurrence of morbidity and mortality of the disease. This system is currently in the raw data evaluation stage.

Pulmonary Function Data System

Judy Mahaffey (DMB/ASPS); Ronald Crystal (NHLBI/IRPB); Larry Nadel (DCRT/LAS). The Pulmonary Branch of NHLBI has requested the development of a combined computerized data base for pulmonary function and exercise testing data to replace existing separate ones. The new system will support studies being conducted by the Pulmonary Branch and will process information on Clinical Center patients with pulmonary complications. It is hoped that the system will interface a NOVA and an LSI-11 mini-computers. Pre-analysis has begun.

Analysis of SLE Data

George Shakarji (DMB/OC); John H. Klippel (NIAMDD). A system has been implemented to store chemistry and therapy data on SLE (Systemic Lupus Erythematosus) patients. In addition to the storage feature the system computes and evaluates routine statistics, at the option of the investigator, to check ongoing trends with respect to certain drugs or therapy.

Statistical Models of Within-person Variation

George Shakarji (DMB/OC); E. K. Harris (DCRT/LAS). Data base for this study involved serial chemistry data from 162 participants in a health monitoring program. Two statistical models for forecasting were applied. One model assumes homeostatic variability over time and the other model assumes nonstationary variation with a high degree of autocorrelation between observations. Forecast ranges were calculated from both models. For this particular study the random-walk or nonstationary model proved to be better at detecting trends.

Evaluation of Chemistry Data of Japanese Normals

George Shakarji (DMB/OC); E. K. Harris (DCRT/LAS); Toshio Yasaka (Japan). This study involves serial measurements of normal Japanese individuals over a period of nine years. Data base includes fifteen to eighteen semi-annual samples of six biochemical tests. Storage and retrieval phases were completed and the analysis of the data has begun. The analysis will involve application of univariate and multivariate time series models to detect and evaluate trends.

Drug Name Validation and Expansion to Active Ingredients System

Mike Lanigan (DMB/ASPS); E. Hadley (NIA). A system has been developed for the Clinical Physiology Branch, NIA Gerontology Research Center, to assist them in aging research. The system computerizes patient data and drug trade name data and provides detail data on active ingredients. This work supports an effort to establish relationships between certain chemicals and the aging process. The system is operational.

Lupus Data Analysis and Retrieval System

George Shakarji (DMB/OC); John Decker (NIAMDD). A group of programs was implemented to analyze laboratory findings on two cohorts of Systemic Lupus Erythematosus study patients. This system is being used to provide ongoing analysis of chemistry results and to advise the research investigator of abnormal trends among his patients.

Tissue Typing Program

B. Cole (DMB/SAS); H. Krakauer (NIAID); K. Hopkins (NIAID). Before this program was developed, the interpretation of tissue typing results was done by various labs using procedures which differ from one another. This system was developed to perform computer analysis of antigen specificity from tissue typing data, enabling the NIAID serum bank to perform the interpretation in a standardized way.

Smithsonian Tick Collection Query/Retrieval

D. Feskanich (DMB/SAS); G. Gautier (Smithsonian); C. Clifford, J. Kearn (NIAID/RML). The Rocky Mountain Lab has catalogued the tick collection on tape and sent the data to the Smithsonian Institution. Ms. Feskanich will be supplying the ability to query the file from Montana using the DCRT central computer facilities.

SCATFIT on the 370

S. Knisley (DMB/SAS); D. Rodbard (NICHD). This set of programs calculates a non-linear least squares curve fit for a Scatchard model. Mr. Knisley has made a number of changes to the programs to bring them up to the state of the art and will be making more changes in the future.

SCATFIT on the DEC-10

C. Creede (DMB/SAS); D. Rodbard, P. Munson (NICHD). This program fits parameters of a non-linear Scatchard plot for one, two, or three classes of independent sites. It has been completely rewritten by Ms. Creede and is now being redistributed to the radio-immunassay (RIA) community.

RIA on the 370

J. Huston (DMB/SAS); D. Rodbard, P. Munson (NICHD). This program, used for computer analysis of radio-immunoassays, was completely reworked and a number of major changes were made. The program is now ready for export. It will be rewritten in BASIC (in a stripped-down version) for use by the PDP-10 community.

Pupillary Response

B. Cole (DMB/SAS); D. Newsome (NEI). Consensual response of the pupils to unilateral stimulation by light flashes as it relates to macular and retinal degeneration is being studied. B. Cole is determining a way of digitizing the wave forms and providing statistical analysis of the results.

Somatic Cell Genetics/Cell Inventory System

B. Cole (DMB/SAS); M. Nirenberg (NHLBI). This computer system allows for keeping inventory information current, locating a desired cell line quickly, identifying the contents of any freezer location, recording cell line usage and history, spotting cell line shortages, and detecting and utilizing any space which becomes available in any freezer.

Liquid Scintillation Counter Package/SCINT

B. Cole (DMB/SAS). This package provides users of scintillation counters an easy method of plotting and analyzing their data. Since its completion last year, it has been adopted by several researchers as one of their basic research tools. Emphasis during FY80 has been on reaching potential system users, particularly those who have computer-oriented applications but are not presently using a computer. A brochure is being distributed for this purpose.

Seroepidemiology Data Processing System

Judy Mahaffey (DMB/ASPS); Paul Levine (NCI). The Clinical Studies Section, NCI Laboratory of Viral Carcinogenesis, is trying to find characteristics of serum samples that can be used to predict cancer. To this end, a computer system has been designed to manage all data necessary for efficient inventory control, test results feedback, and statistical analysis. The system is now operational and reports from the system are being sent to collaborating scientists in the U.S., Ghana, Greenland, and Singapore.

Wild Mouse Breeding Colony Data Processing System

Vivian Pelham (DMB/ASPS); Ernest Plata (NCI). The Laboratory of Viral Carcinogenesis, NCI Division of Cancer Cause and Prevention, breeds and raises a rare and valuable strain of wild Asian mice originally acquired from Vietnam. A system is being developed that will maintain all data collected on these animals and aid in selective breeding, carcinogenesis studies, aging studies, etc.

Canine Breeding Colony Data Processing System

Roger Dailey (DMB/DBAS); Dennis George (DMB/ASPS); T. Wolfly (DRS/VRB/ACS); R. VanWey (DRS). The goal of this project was to develop a system to assist the Veterinary Resources Branch, DRS, with its record keeping and work scheduling. The system is complete. DRS is now in the process of installing a word processor system (CADO) in Poolesville to handle all data entry, maintenance, etc. When this is complete, DMB will work on interfacing the two systems.

Strain Specificities Reference System

Steve Soroka (DMB/ASPS); David Sachs (NCI). A computer system is being developed for the Division of Cancer Biology and Diagnosis, NCI Immunology Branch to assist in transplantation biology research. The system will be used to help locate existing cogeneric mouse strain products and/or to design mouse strain products that have specific antigens which are used in experiments relative to the development of sera. Analysis has been completed and a design proposal is being prepared.

Statistical Support for Image Processing Data

C. Creede (DMB/SAS); J. DeLeo (DCRT/CSL); M. Jones (NHLBI). Ms. Creede has begun a collaboration with Mr. DeLeo to provide a statistical analysis package for use by researchers obtaining data from Mr. DeLeo's image processing system.

Multivariate Time Series Package

George Shakarji (DMB/OC); Eugene Harris (DCRT/LAS). A package that analyzes related data and computes an estimate for the optimum weight matrix for the exponential smoothing and prediction of multivariate time series was developed and tested. The method employed allows the estimation to forget the remote part in order to follow a process in which the structure varies slowly with time. The exponential smoothing is a weighted average of past values of an observed process which gives decreasing weight to past values. Since the weights sum to unity, the smoothed time series has a tendency to follow changing mean values.

Ectromelia Epidemiologic Survey

Dennis George (DMB/ASPS); Gordon Wallace (NIAID/DIR). This project provides the data processing services necessary to determine the environmental factors that most likely contribute to the spread of Ectromelia (Mouse Pox). The data that will be used for this project are currently being collected.

Clinical Modeling on the HP-9845

S. Knisley (DMB/SAS); D. Rodbard (NICHD). A set of small, easy-to-use programs is being developed for clinicians to enable them to obtain printer plots of patient data at the bedside and perform simple statistical computations. Available as the first module is a GROWTH program which was developed mainly to plot growth hormone against response but can actually plot any two-dimensional curve.

Record Keeping System/Dyslipidemia

G. Roberts (DMB/SAS); Dr. E. Schaefer (NHLBI). This system keeps records on clinical and laboratory data for normal and dyslipidemic subjects and provides for routine reporting as well as ad hoc queries and preparation of select subfiles for statistical analysis.

Materiel Management System (MMS)

Marvin Katz, Ron Wicks (DMB). This ongoing administrative project utilizes data base technology in support of NIH-wide procurement, receiving, and payment activities. As the MMS entered its third year of development and operation, much time was spent in enhancing existing software. During FY80 some 50 change control items successfully went into production. New developmental efforts implemented were: (1) the capability to partially pay request order line items through the system; (2) the generation and control of payment schedules that go to Treasury; (3) a prototype delegated procurement entry system for the BID's utilizing teletype compatible terminals; and (4) a basic source data entry and control procedure for blanket purchase agreements and indefinite delivery contracts.

Merit Pay Model

B. Cole (DMB/SAS). Mr. Cole developed a computer model to allow managers, administrative officers, and personnel people to predict merit pay pool allotments and to forecast the impact of performance appraisal ratings on distribution of pay pools for Merit Pay employees.

DRR Grants Subproject System

Vivian Pelham (DMB/ASPS); Jean Babb (DRR). The existing DRR Grants Subproject System that uses CPS is being evaluated. A proposal will be made for the re-design of this system to make use of more current, supportable technology.

NIH Nutrition Grants Monitoring System

Judy Mahaffey (DMB/ASPS); Mike Lanigan (DMB/ASPS); Thomas Vogl (OD). A system has been designed for the NIH Nutrition Coordinating Committee to assist them in monitoring and reporting data on biomedical and behavioral nutrition research at NIH and at other agencies within DHHS. The system is operational and Dr. Vogl's office is currently using it to answer inquiries from NIH directors' offices, the White House, Congress, and the Public as they relate to dollar amounts and percentages of grant money being spent in the area of nutrition.

Review and Evaluation Branch Grants Information System

Penny Brogan (DMB/ASPS); Harry Canter (NCI). The computerized Research Analysis and Evaluation Branch Grants Information System, a highly specialized grants management system, was designed and implemented for the Division of Cancer Grants, NCI. Enchancements are currently being made to the Intramural and Funded Grants subsystems, and the system is being extended to include contract data. In the future, a Training Grants system will be developed.

NIH International Activities and Personnel Monitoring System

Penny Brogan (DMB/ASPS); Mike Lanigan (DMB/ASPS); Libby Low (FIC). A system has been developed to process financial and visa data on the foreign guest workers and foreign visitors at NIH. The Fogarty International Center is currently using this system to provide reports for the Visiting Program, foreign nationals, and foreign embassies. The growth of the current data files will necessitate a future revision of the system to separate current data from historical data.

Employee Health Unit System for Occupational Medical Services

Steve Soroka (DMB/ASPS); Julio Rivera (CC/OMS). A system has been developed to help the Employee Health Unit schedule medical check-up visits for employees in programs that require routine medical monitoring. The system is operational.

Committee on Academic Science and Engineering (CASE) Reports

Darius Georg (DMB/ASPS); J. Bailey (OD/OPPE). This project involves a broad spectrum of data processing support required for the collection and reporting of DHHS obligations to: Institutes of Higher Education, Research and Development Centers, and Non-profit Institutions. This is an ongoing project.

MMS Query and Reports

Jane Blessley (DMB/ASPS). This project is intended to provide an economical method for the selection and reporting of data from the NIH Administrative Data Base. Ms. Blessley provides recurring and ad hoc reports from the data base for all segments of the NIH community.

System for Controlling and Monitoring Complaints of Discrimination at NIH

Darius Georg (DMB/ASPS); G. Yee (OD/DEO); M. Williams (OD/DEO). This project establishes and maintains a file which provides statistical data, on a case by case basis, of formal and informal complaints of discrimination at NIH. In the past year Mr. Georg revised the data base to make a more complete record for each case. He is currently revising and simplifying the retrieval process.

Information System of Bioscientists

Darius Georg (DMB/ASPS); W. Copeland (OD/OPPE); J. Bailey (OD/OPPE). This system is intended to establish and maintain a data base of people who are qualified to serve as members of NIH's initial review groups. In the past year data from numerous sources has been added to the data base. Mr. Georg is currently serving as technical advisor on a committee that is studying how these data can be used by a larger segment of the NIH community.

ARMS/TDCS Interface

Dennis George (DMB/ASPS); B. Hughes (OPA/P); A. Amatucci (OA/M). This project is intended to create an NIH Personnel System which is a composite of the current NIH personnel system (ARMS) and the DHHS Personnel System (TDCS). In the past year the analysis and design of the proposed system was completed. Implementation is awaiting approval of the ARMS Steering Committee.

Radiation Safety Control System

Charles Twigg (DMB/ASPS); R. Zoon (DRS/RSB). This system is designed to monitor the use and users of radioactive isotopes at NIH. When complete, this system will include five subsystems. They are (1) Inventory and Bioassay, (2) Lab Survey and Airborne Release, (3) Waste Processed and Activity Balance, (4) Training, and (5) Film Badges. In the past year Training and Film Badge subsystems were completed and added to the system which previously contained the Inventory and Bioassay subsystem.

HMO Information System

D. Feskanich (DMB/SAS); H. Karch, K. Mason, M. Dudley (OHMO). This system will support the Division of Compliance, Office of the Assistant Secretary of Health in monitoring the legislatively mandated reporting requirements of federally qualified Health Maintenance Organizations. Ms. Feskanich has provided data entry, edit, update, and reporting capability. Future plans include an early warning system on the financial viability of the individual HMO, and feedback to the HMO concerning its status in relation to the rest of the industry.

Electrical Safety Program System

Larry Martin (DMB/ASPS); Charles Twigg (DMB/ASPS); Howard Metz (DRS/BEIB). The chief of Scientific Equipment Services of the Biomedical Engineering and Instrumentation Branch has requested a system to help monitor maintenance of equipment at the Clinical Center. A system is being designed to computerize the results of routine electrical safety checks and preventive maintenance performed on hospital equipment. The system will be used by DRS to schedule equipment checks, to provide reviews on instruments checked by contractors and by the CC, and to provide statistical information on different types and repair histories of equipment.

Dermatology Information System

Steve Soroka (DMB/ASPS); Richard Lymn (NIAMDD/ABSD). A system has been developed to maintain an active file on grants, contracts, and intramural research projects that relate to skin diseases. The system is operational and is currently being used by the NIAMDD Arthritis, Bone and Skin Diseases Program for budget and project management and analysis and to answer congressional and constituent inquiries.

Funding of Women vs. Men in Extramural Research Grants

Jack Heavey (DMB/OC); Stewart Wright (DRG). The purpose of this study is to illustrate the relative status of women in extramural grant-supported research within DHHS, in regard to age, size of project (dollar amount), academic background, type of activity supported, etc., based on data from 113,000 subjects. To date, most of the analysis has involved general linear modeling to analyze the effects of the variables and their interactions. Once the results are reviewed, further computing will begin.

Selective Dissemination of Information

S. Knisley (DMB/SAS). SAS has continued its support of the current awareness search for both Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS). Retrospective searches are referred to the NIH Library staff.

Proposal for Evaluation Project

G. Roberts (DMB/SAS); P. Henry (OD). The purpose of this project is to develop the capability of searching existing NIH data bases for information on awards and research publications indexed by MEDLINE, and to relate these to program management data and information. Mr. Roberts developed a proposal for computerizing these functions.

Chinese Personalities and Institutions in Biomedicine

Judy Mahaffey (DMB/ASPS); Joseph Quinn (FIC); Joseph Lee (FIC). Due to a rapid increase in international exchanges in the field of biomedicine between the U.S. and the People's Republic of China, the Fogarty International Center has requested DMB services to design a system for the computerization of data on biomedical scientists and institutions in the PRC. The system will be used by the FIC officials in briefing NIH and non-NIH scientists interested in biomedical research in China. Pre-design analysis has been completed and a design proposal is being prepared.

SLANG (Structured Language) Compiler

R. Magnuson (DMB/SSS). SLANG is designed to assist programmers to generate block structured assembly language code on the IBM 370. The SYSPRINT output data set was modified this year to improve source code readability. The features added include automatic indentation, generic statement numbering, boxed comments, and program structure display.

Voice Input Support

R. Magnuson (DMB/SSS). As a follow-up to DMB's initial voice input project, this section is examining the feasibility of developing voice input applications by way of micro-processors, which can act as front end processors to larger computers. This year was spent designing a micro-system with plug-in peripherals, purchasing the hardware and becoming familiar with its features.

SFOR (Structured FORTRAN) Compiler

R. Magnuson (DMB/SSS). Designed to assist programmers writing structured programs, the SFOR compiler generates block-structured IBM FORTRAN source code. There are six different kinds of blocks available to the FORTRAN programmer -- CASENTRY, FOR, IF, LOOP, REPEAT, and WHILE.

Intermediate Query Package

John Parks (DMB/SSS). An online query package is being developed to fill the gap between existing interactive retrieval software and the Symbolic Logic Retrieval (SLR) programs. Controlled by a field-name table, the package handles non-hierarchical files and is relatively rigid in its output formatting. The package is currently in the testing and enhancement stage.

MARK IV Forms Collect Program

Joe Campbell (DMB/SSS). To eliminate much of the drudgery of preparing user specification forms for MARK IV, a Timesharing Option (TSO) program was developed to prompt for entries in each MARK IV form and to generate the fixed form output.

MARK IV Transaction-collect Generator

Joe Campbell (DMB/SSS). This software was developed to run under TSO to facilitate the collection of transaction records which update MARK IV master files. The system prompts the user for data fields within the record, formats the selected transaction, and creates a file for master file update.

Products Support

Software Support Section (DMB/SSS). Provides necessary support for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, REFORMATGEN, REPORTGEN, TRANSACTGEN, Standardized Update, Voice Input, SFOR, Inquiry and Reporting System, and MARK IV. This ongoing support includes software maintenance, customer assistance, and the teaching of formal DCRT courses on these products.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00048-01 DMB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Clinical Information Utility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: William D. Vincent Computer Systems Analyst DMB DCRT

COOPERATING UNITS (if any)
Clinical Center, Office of the Director

LAB/BRANCH
Data Management Branch

SECTION
Clinical Support Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5.0		

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Clinical Information Utility System is a clinical data base management system which was specially designed to collect, organize, archive, and retrieve clinical data for patient care and research at the National Institutes of Health in Bethesda, Maryland. The system architecture is an integrated set of subsystems. The subsystems perform the functions of data entry, management, and retrieval.

Projects and Activities
FY 1980
Computer Systems Laboratory

Alan M. Demmerle, Chief

Computer Support for Flow Microfluorimeters/Cell Sorters (NCI, NIAID, NHLBI): In FY80, CSL continued support for a FACS-11/PDP-11/34 FMF system (NCI/I) and a Los Alamos Scientific Laboratory (LASL)PDP-11/34 FMF system (NCI/LP). A FACS-II/PDP-11/34 system was delivered in FY79 for NIAID/LMI and became operational in FY80. NHLBI/CHB decided that their needs would be best fulfilled with a FACS-II/PDP-11/34 system identical to the other two at NIH. This system was ordered in FY80. A FACS-II is being ordered to replace the LASL FMF. The major effort in FY80 was the conversion of RT-11 programs to run under RSX-11M. In June 1980, the four major display and analysis programs were running under RSX-11M with essentially the same features that were available under RT-11.

Cardiac Scintillation Probe (CC, NHLBI): CSL has continued the development of its Cardiac Scintillation Probe, originally started in 1977. This non-imaging, ECG-gated probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and LV pressure. Parameters such as LV compliance can be continuously monitored. This year, the previously implemented capability for real-time pressure-volume measurements were used to study the effect of verapermil on patients with asymmetric septal hypertrophy. It is anticipated that the quantitative pressure-volume relationships produced by the probe system will be able to better characterize the effects of the drug. Pressure-volume changes were analyzed to determine the best parameters for automatic calculation and presentation by the system and specific software was developed for this application. An additional detector to allow for simultaneous background and left ventricle volume measurements was added and this new capability is being evaluated.

Nuclear Medicine Computer Systems (CC): CSL has continued consultation and support for the imaging systems located in the Nuclear Medicine Department. This involved working with Nuclear Medicine to assess their clinical computing requirements in regard to anticipated growth with the new Ambulatory Care Facility. This year, the Nuclear Medicine distributed computer system was extended to include all the existing imaging systems in a single network. CSL also worked with Nuclear Medicine to implement a new display system. The new display provides increased capability for more sophisticated data presentation and for transmission of the images for daily and weekly clinical conferences.

Computerized Radiation Therapy (NIC): CSL has developed a computer system, now is operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. The system allows the radiation therapist to review scans of the tumor area at a color video terminal, quickly varying the presentation or the image to emphasize a particular structure or to magnify an interesting feature. Outlines of tumors or vital organs, in some cases drawn automatically by computer, are then processed by software purchased from Atomic Energy of Canada, Ltd. to provide sophisticated individualized treatment plans.

Cardiac Intensive Care Unit Patient Monitoring Computer System (NHLBI): The Surgery Branch of NHLBI has collaborated with CSL on a continuing basis in the development of automated techniques for monitoring patients in a post-operative cardiac intensive care environment. Previous annual reports describe the details of the system's functional goals and project milestones. Minor software changes were implemented early this reporting period, and software development was then terminated. The final hardware effort was the implementation of computer-control of the hard copy unit located within the intensive care unit, from commands issued on bedside keyboards. The system is currently maintained in continuous operating by CSL staff, however, all system development was completed this year.

Medical Intensive Care Unit Patient Monitoring Computer System (CC): This project involves the development of an automated patient monitoring system for measurement, analysis, control, and record-keeping functions in a nine-bed medical intensive care unit. A minicomputer-based patient data management system, a cardiovascular research susbsystem, a software development subsystem, and a medical mass spectrometer subsystem are already operational. A large field-of-view scintillation camera system for obtaining images of the cardiovascular and respiratory system will be added to the unit. Future project goals involve the development of respiratory system monitoring, non-invasive measurements of the cardiovascular and respiratory systems, computer controlled drug infusion, and automated urine output measurement. A data base of the patient information obtained with the systems will be created and used for retrospective studies by the medical staff.

The Biomedical Image Analysis Project (NCI, NHLBI, NINCDS, NIMH): This project is oriented toward the development of general-purpose algorithms and techniques for image digitization, contrast enhancement, edge detection, contour extraction, contour following, contour coordinate data compression, and three-dimensional representation. The resultant general-purpose capability is being accomplished through work with a number of NIH researchers who encounter relatively similar classes of problems in unique individual settings.

Automated ECG Processing (CC): The Clinical Center's ECG Service requires and online ECG computer system to assist staff physicians in analyzing and reporting current ECG's comparing serial ECG's and conducting research data processing and intercharge. CSL prepared a request for proposals for a mini-computer-based ECG system in FY79. CSL and LAS participated this year, with Clinical Center staff members, in the evaluation of vendor's proposals. Delivery and installation of the system is expected in FY81.

Automated Pulmonary Exercise Testing (NHLBI): The pulmonary treadmill/exercise testing laboratory is being automated for monitoring and analysis of parameters such as oxygen consumption, work of breathing, and pulmonary compliance. This year, a microcomputer system was selected and ordered for this purpose, the initial test protocol was designed, and software development was begun using CSL's development facilities.

Pulmonary Branch Support (NHLBI): This project involves assisting the Pulmonary Branch to meet its computer and data processing needs. This year CSL coordinated the purchase and installation of two new automated pulmonary function analyzers, and worked with DMB to interpret PB's record keeping and reporting needs for use in developing a clinical data base. During FY81, we expect to interface the pulmonary function analyzers to the data base system to be developed by DMB. Results from the Automated Pulmonary Exercise Testing project (reported separately) will be similarly interfaced.

Otoadmittance Data Logger (NINCDS): A microprocessor-based data logger was designed and built to continuously sample the analog signal from an otoadmittance meter, and record that data on digital cassette tape. Once recorded the data can easily be played back to a computer for analysis by PSL. A spin-off from this project is an improved design for a cassette tape interface board now being used for specialized data logger projects. This work should lead to substantially reduced development time for similar future applications, and to the subsequent design of a physically smaller data logging system in response to the problem of limited laboratory space at NIH.

Computer Interfaces for Clinical Laboratory Instruments (CC): A new method has been developed to interface clinical laboratory instruments to the existing clinical laboratory computer system. By using microprocessor-based interfaces and standard serial communicating tenchniques, new instruments are easily interfaced. If the computer system needs to be upgraded or replaced at some future time, it should only be necessary to change the processor communication software to connect the instruments to the new computer. This year, a new Coulter Model S-Plus cell counter was interfaced in this way. Design of a microcomputer assisted, multi-station system for white cell differential counting is now underway.

LABORATORY INVESTIGATION

Distributed Laboratory Data Acquisition and Control System (NIAMDD): A Distributed Laboratory Data Acquisition and Control System (DLDACS) has been implemented for NIAMDD, in Building 2, as a replacement to the Laboratory Computer System developed by CSL ten years ago. The new system consists of a network of remote microcomputers connected in a star configuraion through a communications processor to a central data processing computer. The remote microcomputers handle all of the realtime data acquisition requirements and provide instrument control functions when required. The collected data is normalized, buffered, and transmitted at a convenient time to the communications processor as files over a serial line, using a standard block communications protocol. The communications processor serves as a store and forward front end for the central computer. Five instruments have been coupled via LDACS to the local network. One remaining instrument from the former system is in the process of being converted and requests for connecting two new instruments have been received. A PDP-11/70 was installed recently as the host computer replacing the old H-516.

Molecular Interactions Laboratory Data System: Analytical Unltracentrifuge, Circular Dichroic Spectropolarimeter, Laser Light Scattering Instrument (NHLBI). When fully implemented, this system will facilitate the acquisition and processing of information from an anlytical unltracentrifuge, a circular dichroic spectropolarimeter, and a laser light scattering instrument. These tools are used to investigate the interactions between human lipoprotein subunits. Current capabilities include acquisition, display, and preprocessing of data from the ultracentrifuge and transfer of preprocessed data files to the central NIH DECsystem-10 for further analysis. The complex nonlinear analyses necessary for the characterization of interacting systems will be done using MLAB on the DECsystem-10. Computation of molecular weights for non-associating systems can be performed locally in the microcomputer. A commercially available hardware/software package, which will automate the laser light scattering instrument and be compatible with the microcomputer, is being evaluated.

Californium-252 Plasma Desorption Mass Spectrometer Data System (NHLBI): A Californium-252 plasma desorption mass spectrometer is being built for NIH by Dr. Ron MacFarland who is with the Texas A&M University Chemistry Department. Delivery is scheduled for the summer of FY80. This instrument puts unusually and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations. A data system design specification that meets these requirements has been drawn up and an evaluation of available hardware and software is underway. Special interface electronics that will be required are being fabricated through a Texas A&M subcontract.

EDS-WDS-Scanning Electron Microscope System (NIAMDD): Following the recommendations of CSL, Dr. William Hagins of NIAMDD initiated procurement of a combined energy-dispersive (EDS) and wavelength-dispersive (WDS) X-ray analysis system for a scanning electron microscope. Since no single vendor marketed a suitable combined EDS-WDS system, the supplier of the EDS has integrated its PDP-11/34-based system with a WDS from another vendor. The final system can perform stand-alone analysis as well as acquire and transmit data to the DECsystem-10 for further computation. After a number of delays on the part of the WDS vendor, compounded by equipment failure on the microscope, the system has been completely installed, the software has been verified and analyses are now being performed.

Radiation Counter Data Recorder: A contract was awarded for the manufacture of Radiation Counter Data Recorders developed by CSL. The initial quantity of about 25 data recorders have been delivered, bringing to nearly 50 the number in use with liquid scintillation counters and gamma counters in laboratories throughout NIH. CSL is now trying to establish a contracting mechanism by which investigators can easily order additional data recorders by a deliver order or a record of call. An agreement is also planned whereby the Systems Maintenance Section, DRS/BEIB wil provide maintenance for data loggers in the future.

Measurements of Transepthelial Resistance of Kidney Tubules (NHLBI): A microcomputer-based instrument was developed to facilitate determination of the transepithelial resistance of an in vitro preparation of kidney tubule. The instrument controls the onset, intensity, and duration of a series of electric current pulses through the preparation, and measures the resulting voltages at each end of the tubule. Presently the instrument prints the currents and voltages from which the investigator must calculate the resistances and other parameters of interest. Plans call for enhancing the instrument to perform these calculations as well.

Electron Microanalysis Facility (DRS): CSL in collaboration with DRS/BEIB is developing an automated microanalysis facility consisting of two electron microscopes interfaced to a PDP-11/60 computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will be used for the acquisition and display of spectra and images resulting from electron energy loss spectrometry and x-ray spectrometry.

Metabolic Energy Measurements (NHLBI): A microcomputer-based instrument is being developed for the direct and indirect measurement of parameters associated with aerobic respiration. DRS/BEIB is designing an interface for a set of electrodes and CSL is developing the microcomputer and software to perform the direct measurements and the calculations needed for the indirect measurements. The system will be used to study energy transduction phenomena due to respiration in biological cell preparations in an aqueous solution.

PROGRAM MANAGEMENT AND ADMINISTRATION

Library Automation Project (DRS): This project is directed toward automating the major functions of the NIH Library. In response to the CSL study reported on in FY79, the NIH Library has decided to purchase the available elements of an automated total Library system. As no currently procurable system is expected to meet all NIH Library specifications, CSL expects to adapt a purchased system to unique Library requirements. During the past year, CSL has exhaustively studied Library needs and generated a comprehensive Request for Proposals covering hardware, software, and conversion of Library holdings to machine readable form. System installation is anticipated for late Spring '81, at which time CSL's development effort should be underway.

BIOMEDICAL COMMUNICATIONS APPLICATIONS

Voice Output Terminal for the Blind: A microcomputer, a speech synthesizer, and an English text-to-speech conversion algorithm have been combined to form a voice output terminal for blind computer users. Following development of a prototype terminal in FY79, we incorporated several design improvements this year. Three terminals were assembled and are improving the productivity of blind computer programmers who are employees of the Federal Government. CSL is investigating additional enhancements which may open more employment opportunities for blind computer users.

Bioassay Information System (NCI, FDA/NCRT): The National Center of Toxicological Research, through an interagency agreement, is developing a data base system called the Toxicology Data Management System for use by NCI's Bioassay Program in performing long term animal studies on potential carcinogens. CSL has consulted with NCTR and NCI since FY77 on specifications for microcomputer based programmable data acquisition terminals that will be a part of this system. This year, CSL has helped in the evaluation of proposals for these terminals. The Laboratory expects to continue its consulting role by helping to monitor contractor performance until the first group of terminals is delivered.

COMPUTER RESEARCH AND TECHNIQUE DEVELOPMENT

Image Processing Facility: This project, begun during the reporting period, is intended to provide a facility to display and analyze digital images. The project has identified a number of potential users from among those currently pursuing image processing on the campus, and from among other interested scientists in the NIH community. General specifications drawn up by CSL for such a system have bee presented to these users for comments and suggestions and, after subsequent discussion, procurement of a computer-display system has been initiated.

Communications Link: CLINK (Communications Link) is a software system for transferring files via asynchornous telecommunications lines between the DECsystem-10 and PDP-11 minicomputers. CLINK was developed as a joint project of CSL and CCB. This year CLINK was extended for use with additional PDP-11 systems, several enhancements were added, the documentation was updated, and the revised package was distributed to users.

Medical Information Technology Project: This project involves evaluating improved man-machine interface methods and identifying ways that modern microprocessor technology might benefit physicians and the practice of medicine. Interface methods that offer promise are voice input/output, bar codes (such as used with point of sale equipment), and touch screen selection systems for use with video displays. Potential applications include medical record keeping, medical education, and computer-aided diagnosis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00050-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computer Support for Flow Microfluorimetry/Cell Sorters (FMF)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Robert J. Romanoff	Computer Specialist	CSL, DCRT
OTHER:	Arthur R. Schultz, Jr.	Processor Design Section	CSL, DCRT
	Irving Levy	Electronics Engineer	CSL, DCRT
	Eric S. Loiderman	Computer Aid	CSL, DCRT
	Leonard N. Zubkoff	Mathematician	CSL, DCRT
	Susan O. Sharrow	Chemist	I, NCI
	John R. Wunderlich	Senior Investigator	I, NCI
	Virginia T. Hamilton	Biologist	LP, NCI
	Thomas M. Chused	Senior Investigator	LMI, NIAID

COOPERATING UNITS (if any)

I, NCI: LP, NIC: CHB, NHLBI: LMI, NIAID

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 2.9
PROFESSIONAL: 1.0
OTHER: 1.9

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project provides dedicated PDP-11 computer support for two Becton-Dickinson FACS II Flow Microfluorimeter (FMF)/Cell Sorters and one Los Alamos Scientific Laboratory (LASL) FMF. Data acquisition is via an NIH designed interface to the computer. Data display and analysis for high sample thruput is the principal system feature. Software currently running under the RT-11 operating system is being converted to function under the RSX-11M operating system in order to allow more effective support of current and anticipated workloads. New hardware and software capabilities are being added during the conversion effort.

Background and Objectives:

Since FY 75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display and analysis needs of investigators using Flow Microfluorimeters (FMF's) at NIH.

In FY 80 CSL continued support for a FACS-II/PDP-11/34 FMF system (I, NCI) and a Los Alamos Scientific Laboratory (LASL)/PDP-11/34 FMF system (LP, NCI). The FMF's are connected to the computer via an NIH designed interface. A FACS-II/PDP-11/34 system was delivered for LMI, NIAID and became operational in FY 80. In FY 79, an evaluation of existing and anticipated requirements for the two FACS FMF systems resulted in CSL recommending that software running under the RT-11 single user operating system undergo conversion to function under the RSX-11M operating system. To support RSX-11M it was also recommended that the NCI PDP-11/40 computer be replaced with a PDP-11/34 and additional memory and data storage capabilities. This equipment was installed in FY 80. It was also recommended that a new and faster incremental plotter made by Zeta be purchased for the two RSX-11M based systems.

Progress in FY 80:

Software capabilities added to the RT-11 based systems in FY 80 included (1) a new and significantly more versatile version of a program that converts raw data information on magnetic tape to distributions on disk files according to the investigators specifications, and (2) providing for all analysis programs to print results on a line printer if available.

The major software effort in FY 80 was the conversion of RT-11 programs to run under RSX-11M. In June, 1980 the four major display and analysis programs were running under RSX-11M with essentially the same features that are available under TR-11. The plotting program had also been rewritten to support the new Zeta plotters. An initial version of a data acquisition program for RSX-11M has been provided by LMI, NIAID. During the summer of 1980, new features were added to all programs in order to take advantage of the RSX-11M environment. Software mechanisms that allow the user convenient access to the programs will also be developed. It is anticipated that by the end of FY 80, the RSX-11M system will be available.

Several hardware modifications were made by CSL to the FACS-II FMF systems during FY 80. These modifications include: (1) redesign of part of the interface to sense FMF gain control settings, and (2) adding a third gate and sort parameter to increase instrument versatility.

Proposed Course:

As a result of a request from CHB, NHLBI for assistance in configuring a new FMF system and the announcement by Becton-Dickinson of the FACS IV FMF which has an integral microcomputer, CSL performed a detailed comparison of five alternative systems involving various configurations of FACS-II and FACS-IV FMF's in combination with PDP-11/34 computers. As a result of this study, CHB, NHLBI decided that their needs would best be fulfilled with a FACS-II/PDP-11/34 system identical to the other two at NIH. This system was ordered in FY 80.

In the forthcoming year, CSL plans to assist in installing the NHLBI system, and continue to add useful functions to the software used on all FMF systems that CSL supports.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00051-01 CSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cardiac Scintillation Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Harold Ostrow	Electronics Engineer	CSL, DCRT
OTHER:	Scott Allen	Medical Research Analyst	CSL, DCRT
	Steve Bacharach	Physicist	NM, CC
	Michael Green	Physicist	NM, CC
	Robert Bonow	Cardiologist	CB, NHLBI

COOPERATING UNITS (if any)

Nuclear Medicine, CC, Cardiology Branch, NHLBI

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.3	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. This non-imaging ECG-Gated scintillation probe, when used in conjunction with left ventricular (LV) catherization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored. This year the previously implemented capability for real-time pressure-volume measurements were used to study the effect of verapermil on patients with asymmetric septal hypertrophy. It is anticipated that the quantitative pressure-volume relationships produced by the probe system will be able to better characterize the effects of the drug. Pressure-volume changes were analyzed to determine the best parameters for automatic calculation and presentation by the system and specific software was developed for this application. An additional detector to allow for simultaneous background and left ventrical volume measurements was added and this new capability is being evaluated. We are presently investigating the development of a small camera system which will combine the probe with a left ventricular image to ease probe placement and extend its application.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00052-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computerized Radiation Therapy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Hal Fredrickson	Computer Systems Analyst	CSL, DCRT
	William Risso	Electronics Engineer	CSL, DCRT
	Daniel Syed	Chief, Systems Design Section	CSL, DCRT
	Eli Glastein	Chief, Radiation Oncology Branch	DCT, NCI
	Thomas N. Padikal	Senior Physicist	ROB,DCT, NCI
	Joel Tepper	Senior Investigator	ROB,DCT, NCI

COOPERATING UNITS (if any)

Radiation Oncology Branch, NCI

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

CSL has developed a computer system, now in operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning.

The system allows the radiotherapist to review scans of the tumor area at a color video terminal, quickly varying the presentation of the image to emphasize a particular structure or magnify an interesting feature. Outlines of tumor or vital organs, in some cases drawn automatically by the computer are then processed by software purchased from Atomic Energy of Canada, Ltd. to provide sophisticated individualized treatment plans.

Background and Objectives:

The objective of this project is to develop a general purpose computer facility to aid in the planning of radiotherapy dosage by providing better information to commercially available algorithms, and to improve on those algorithms to further refine the planning. The system has been designed for use by medical technologists in routine patient care.

Significance to Biomedical Research:

The Computer System permits radiotherapists to make use of patient-specific information from diagnostic imaging systems in therapy planning. Planning radiotherapy treatment rapidly and accurately allows a large and varied patient mix to receive timely therapy, expanding the depth and breadth of the research possible.

Progress in FY 80:

Training personnel to operate the system continued during the year, particularly among the new employees at the ROB.

An extension of the system, to include the information available in ultrasonic scans, was pursued. ROB has initiated procurement of an ultrasonic scanner, and considerable thought has been given to the inclusion of the scans in treatment planning.

Available methods for management of the data base consisting of information regarding the therapy course were examined, including procurement of further software from Atomic Energy of Canada and subscription to an NCI data management system. CSL has advised that the most useful course at present is to utilize the existing NCI data management system, and ROB is currently doing so.

Proposed Course:

Work will proceed in three basic areas during the next year. The existing system will be converted to a multi-user configuration in order to satisfy an increased demand; further development in the area of ultrasound is expected; and the current algorithms will be substantially updated. The author of a truly three-dimensional treatment planning system has recently jointed the ROB staff, and conversion to that system is anticipated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00053-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cardiac Intensive Care Unit Patient Monitoring Computer System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Kenneth M. Kempner	Electronics Engineer	CSL, DCRT
	Andrew G. Morrow, M.D.	Chief, SB	SB, NHLBI
	Charles L. McIntosh, M.D.	Senior Surgeon	SB, NHLBI
OTHER:	William L. Risso	Electronics Engineer	CSL, DCRT
	Robert L. Martino	Electronics Engineer	CSL, DCRT
	Lee Freeman	Computer Programmer	CSL, DCRT

COOPERATING UNITS (if any)

Surgery Branch, NHLBI

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The computerized patient monitoring system developed in conjunction with Surgery Branch, NHLBI, provides real-time, beat-to-beat analysis of physiologic waveforms from patients within a four bed intensive care unit. Based around a Xerox Sigma-3 Computer, the system monitors the electrocardiogram, arterial and venous blood pressures, body temperature, urine output, blood loss, as well as thermal and dye-dilution cardiac output.

A Morphology Analysis of the electrocardiogram and arterial blood pressure waveforms is performed to detect fiducial markers. The application of cross-correlation techniques to the electrocardiogram allows the detection of premature ventricular contractions. Beat-to-beat data from the most recent thousand electrocardiographic complexes may be recalled at any time in the form of Joint Interval Histograms and Correlation Coefficient Scatter Diagrams. A five-minute electrocardiogram memory is maintained in real-time for use in the detection of transient ventricular arrhythmias. Vital signs are retrievable as eight-hour nursing shift summaries in tabular form, or as 12, 24 or 72 hour vital signs graphs.

Background and Objectives:

The principal objective of this long-term project was to investigate new approaches to the problem of providing an automated patient monitoring environment. More specifically, project goals include the release of the nursing staff from routine clerical tasks, the uniform collection of all vital signs at high frequency, the automated detection of potentially life-threatening ventricular arrhythmias, and the development of an on-line tool for the evaluation of signal processing algorithms.

Methods Employed:

A general-purpose process-control computer system was chosen as the central element of the interactive patient monitoring system. The Xerox Sigma 3 computer was interfaced to a high-speed 16-channel video generator system. Commercially available bedside electronic modules were chosen to provide for the monitoring of all relevant physiologic parameters. Transducers were developed to monitor urine output and blood loss (chest drainage). Active analog and digital transmission lines were fabricated to connect the intensive care unit with the computer room.

The operating system provided with the Xerox Sigma-3 was extensively modified to provide a more suitable environment for real-time, beat-to-beat patient monitoring tasks. Many signal analysis programs, and a sophisticated graphics package were written to accomplish the functional specifications selected for this system.

Major Findings in FY80:

The final phase of system development was completed this past year, although the system has been in continual use on a 24-hour basis for more than four years. Overall this project has shown that it was possible to successfully combine the attributes of a beat-to-beat arrhythmia monitoring system, usually found in a coronary care environment with a periodic data-logging monitoring system, usually found in a general intensive care unit.

The use of a five-minute electrocardiogram memory was found to be valuable aid in the identification of short-lived transient arrhythmias.

Significance to Biomedical Research:

The computerized patient monitoring system can be practically applied to the continuous collection of data for research protocols.

The novel approach to the monitoring of cardiac arrhythmias implemented on this system is easily adaptable to other computer systems with waveform capture capability. These arrhythmia monitoring techniques should prove useful in many clinical and experimental animal protocols, such as drug evaluation studies.

Proposed Course:

Operation of the computerized monitoring system will continue until at least December 1980, when the Surgery Branch's Intensive Care Unit is scheduled to occupy new quarters within the NIH Clinical Center. Plans for transfer or replacement of the system are not complete.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00054-01 CSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Medical Intensive Care Unit Patient Monitoring Computer System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.M. Kempner	Electronics Engineer	CSL, DCRT
	R.L. Martino	Electronics Engineer	CSL, DCRT
	B.D. McLees	Chief, Critical Care Medicine	CCMD, CC
OTHER:	A.J. Pashayan	Computer Specialist	CSL, DCRT
	J.R. McClellan	Assistant Chief	CCMD, CC

COOPERATING UNITS (if any)

Critical Care Medicine Department, Clinical Center

LAB/BRANCH

Computer Systems Laboratory

SECTION

System Design Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the development of an automated patient monitoring system for measurement, analysis, control, and record keeping functions in a nine bed medical intensive care unit. A minicomputer-based patient data management system, a cardiovascular research subsystem, a software development subsystem and a medical mass spectrometer subsystem are already operational. A large-field-of-view scintillation camera system for obtaining images of the cardiovascular and respiratory systems will be added to the unit. Future project goals involve the development of respiratory system monitoring, non-invasive measurements of the cardiovascular and respiratory systems, computer controlled drug infusion, and automated urine output measurement. A data base of the patient information obtained with the systems will be created and used for retrospective studies by the medical staff.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The Medical Intensive Care Unit (MICU), which is administered by the Department of Critical Care Medicine in the NIH Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a 5-bed ward area, a 2-bed special study area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring, respiratory system monitoring, and noninvasive measurements of the cardiovascular and respiratory systems. In addition, the medical staff is performing studies on right heart and pulmonary circulation physiology.

In support of these goals four computer systems have been installed to date: 1) a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information on-line, and keeping medical records; 2) a Cardiovascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results on-line, and generating a catheterization report; 3) a Software Development Subsystem used for developing software for the above described systems; and 4) a Medical Mass Spectrometer Subsystem used for monitoring both the patient airway gases and the gases delivered by the patient's respirator at all nine beds. Featuring the same minicomputer, the first three systems were purchased from the Hewlett-Packard Corporation. The Chemetron Corporation manufactures the microprocessor-based mass spectrometer system.

Major Findings:

The automation of the MICU has aided the medical staff by managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, controlling care room devices, and allowing measurements that would not otherwise be possible.

Significance to Biomedical Research:

Many hospitals around the world are automating various functions in their intensive care units. In particular, the Hewlett-Packard computerized patient monitoring system purchased for this project has been installed in many private, university, and government hospitals. Therefore, any new developments made on this project will benefit many users of automated systems, as well as patient care and clinical research within the MICU at NIH.

Progress in FY80:

The four computer systems have been in continuous operation for the past year. A software package that generates eight and twenty-four hour flow sheets have been developed for the patient data management system. These flow sheets contain both automatically and manually entered data and provide the medical staff with a convenient record that can be used to manage the critically ill patient. In order to allow the entry of the data required for the flow sheet, new data entry forms were added to the system. For example, a form for entering the respiratory gas concentrations measured by the medical mass spectrometer system as well as other respiratory parameters is now available.

A large-field-of-view scintillation camera system for obtaining images of the cardiovascular and pulmonary systems was procured from Searle Radiographics. This system includes both a microcomputer-based console that acquires, stores, processes, and displays the nuclear images, and film recorder that records images, data, curves, and annotations on X-ray sheet film. An analog-to-digital converter for digitizing camera outputs and a display system for presenting images was purchased from the Hewlett-Packard Corporation and will be connected to the development computer subsystem. This minicomputer system will allow programs developed by the Nuclear Medicine Department of the Clinical Center to be used with the new camera as well as the development of new software. In order to obtain a hard copy of the displays generated by the system, a video frame buffer was purchased that will transmit the images to the Searle film recorder.

A portable respiratory cart that provides the transducers and instrumentation needed to measure both respiratory flow and pressure was configured for monitoring pulmonary mechanics. The capability of measuring acetylene and carbon monoxide concentrations was added to a second portable medical mass spectrometer.

Proposed Course:

In the coming year additions will be made to the patient monitoring system. The software needed to automatically measure urine output will be developed while the scales needed to weigh the urine containers are attached to the beds and connected to the computer. IMED microprocessor controlled infusion pumps that allow two-way communication with the central minicomputer will be interfaced to the system. Algorithms that determine the rate of infusion based on the values of the physiologic parameters to be controlled will be developed for continuous intravenous infusion therapy.

The components of the scintillation camera system will be integrated and installed, and the system will be put into operation. Software that has been developed by the Nuclear Medicine Department of the Clinical Center will be added.

With the newly acquired respiratory cart and upgraded portable mass spectrometer, new respiratory system measurements will be developed and evaluated. These include pulmonary mechanics, lung diffusing capacity, pulmonary capillary blood volume, pulmonary capillary blood flow, and pulmonary tissue volume.

Publications:

Martino, R.L., Kempner, K.M., McClellan, J.R., and McLees, B.D.: Automation of a Medical Intensive Care Environment with a Flexible Configuration of Computer Systems. Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care; November 1980 (in press)

McClellan, J.R., Adai, N.E., Kempner, K.M., Martino, R.L., Pashayan, A.J., and McLees, B.D.: A comprehensive Computer Generated ICU Flow Sheet. Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care; November 1980 (in press)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00076-01 CSL

PERIOD COVERED
October 1, 1970 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Image Analysis in Computerized Tomography (CT) Contrast Material Evaluation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Michael Vermess	Radiologist	DR, CC

COOPERATING UNITS (if any)

Diagnostic Radiology (DR), CC

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The intent of this project is to provide a tool for the quantative analysis of liver and spleen section of computerized tomograms (CT) to demonstrate efficacy of a new experimental contrast material which was developed at the NIH Clinical Center as an aid in the demonstration of early metastic disease of the liver. Software for performing this analysis is fully operational on the Image Processing System. Measurements are being made on pre- and post-injection tomograms as they become available.

Background and Objectives:

The objective of this project is to provide a procedure for performing statistical analysis of attenuation values lying within any specified closed amorphous contour of computerized tomogram (CT) images. This procedure is to be used for quantitative analysis of liver and spleen sections of CT images in order to demonstrate the efficacy of a new experimental contrast material which was developed at the NIH Clinical Center to aid the demonstration of early metastic disease of the liver.

Methods Employed:

CT images are transported by means of magnetic tape from the Diagnostic Radiology Department (DR) of the Clinical Center to the Image Processing Facility in the NIH Division of Computer Research and Technology (DCRT). Interactive software has been written and implemented to read the CT images from magnetic tape, draw selected contours to indicate areas of interest, and perform statistical analysis on the attenuation values within the chosen areas. Liver and spleen sections of pre- and post-injection images are processed and compared.

Significance to Biomedical Research:

Most current CT computer systems provide limited statistical analysis within small fixed-shape contours (circles or squares). The approach presented here offers unlimited analysis within any shape contour. The software may be easily extended to measure other features based on groupings of attenuation values; such features could be useful in further differentiating image elements and diseased areas. The software has obvious extension to the analysis of other types of biomedical images.

Proposed Course:

Analysis of liver and spleen sections on pre- and post-injection tomograms are continually being performed as images are made available. It is intended to explore the usefulness of other features derived from computations on clusters of attenuation values.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00055-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Pulmonary Exercise Testing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Lawrence D. Nadel, Ph.D.	Staff Fellow	PDS, CSL, DCRT
OTHER:	Brendan A. Keogh, M.D.	Expert	PB, IR NHLBI
	Perry S. Plexico,	Chief, Project Development Section	CSL, DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Exercise testing methods are being developed for the evaluation of pulmonary function. By exercising a patient on a treadmill and gradually increasing the workload (e.g. speed and incline), the physician can determine the patient's pulmonary reserve. In this way, pulmonary dysfunction, which in its early stages generally does not manifest itself except under physical exertion (i.e. depletion of pulmonary reserve), can be detected and subsequently treated. A microcomputer system is being designed to automate the collection and analysis of the exercise data. In addition, the computer system will automate pulmonary compliance and work of breathing studies.

PHS-6040
(Rev. 10-76)

Background and Objectives:

Physicians have begun to monitor pulmonary parameters during exercise to better assess pulmonary function and to diagnose pulmonary dysfunction that only manifests itself under physical exertion.

Pulmonary treadmill exercise testing is now done manually at NIH. Data is written down and later entered into a programmable calculator for calculation of results. Additional summary statistics are prepared by hand. Work of breathing and static and dynamic pulmonary compliance measurements, done in the same lab, are likewise performed manually.

In order to speed both exam and data analysis time and to improve accuracy, these procedures are being automated with a microcomputer system.

Methods:

The microcomputer system is a DEC MINC-11 (Modular INstrument Computer) containing and LSI-11 microprocessor, 32K words of memory, auxiliary disk storage, and analog-to-digital and digital-to-analog conversion capability. There is also a video graphics display, a keyboard console, and a hardcopy unit for printing the video display.

For an exercise procedure, the computer will monitor expired volume and flow via a tissot spirometer and pneumotach, respectively. Inspired and expired oxygen, carbon dioxide, and nitrogen concentrations will be monitored via a Perkin Elmer gas spectrometer. Acid/base and gas concentrations will be determined off line from a sample of the patient's arterial blood, and will be entered at the keyboard. Pulmonary volumes, flows and oxygen consumption-- a measure of how hard the patient actually works to perform a given level of exercise-- will then be calculated.

Progress in FY 80:

An analysis of computer reuqirements, leading to the selection of the MINC-11 micrcomputer, was performed. The computer was ordered; delivery is expected during September 1980. Test protocols, displays, and report formats were designed, and software development was begun using CSL's microcomputer development facilities. A MINC-11 similar to that purchased was borrowed so that initial design work on graphics presentations could be started.

Proposed Course:

We will begin using the new MINC-11 for patient studies in the exercise lab early in FY 81. Once we are satisfied with its performance in automating the data acquisition, calculation, display, and reporting for exercise studies and compliance and work of breathing determinations, we plan to include closed loop computer control of treadmill speed. By monitoring heartrate and dynamically varying the treadmill speed, it should be possible to apply a more constant workload on the patient, thus leading to more stable results.

We also plan to investigate the value of determinations not presently feasible, such as breath by breath (rather than average) calculations. More comprehensive monitoring of the patient will enable the physician to closely examine the rate and means by which the patient's cardiopulmonary system responds to physical exertion.

Finally, we plan to develop a way of transmitting all patient data to DCRT's IBM 370 computer for automatic storage in the pulmonary data base system presently under development.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00056-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Distributed Laboratory Data Acquisition and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John Powell	Electronics Engineer	CSL, DCRT
OTHER:	Bill Jennings	Physicist	LCP, NIAMDD
	Ron Fico	Electronics Engineer	CSL, DCRT
	Gene O'Bryan	Electronics Engineer	CSL, DCRT
	Arthur R. Schultz, Jr.	Processor Design Section	CSL, DCRT

COOPERATING UNITS (if any)

LCP and LMB, NIAMDD

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A local computer network has been developed at the National Institutes of Health (NIH) as part of an integrated laboratory data acquisition and processing system. This network is configured with satellites connected in a star configuration to a host processor. At each satellite a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The hub of the network, the concentrator utilizes DMA hardware on all communication links and performs a file store and forward function. The local network allows the host storage medium to appear as a "virtual" storage device to the satellites.

PHS-6040
(Rev. 10-76)

Background and Objectives:

A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in Dec. 1976 as the best system architecture of upgrading laboratory data processing. A prototype laboratory data acquisition and control (LDACS) computer and the essential elements of the communication system have been developed.

Satellites perform the real-time data acquisition, and instrument control functions. They are configured with: Digital Equipment Corp. (DEC) LSI-11 microcomputer, 28K words memory, low density random access storage graphics terminal, and all the necessary I/O hardware to interface the instrument/experiment. Satellite software runs under DEC's RT-11 real-time operating system. A hardwired serial link connects a satellite to the concentrator. Although each satellite is capable of stand-alone operation, the immediate transfer of the files allows data processing to proceed on the host system simultaneously with data acquisition on the satellite system. The host processor, a DEC PDP 11/70, is configured with: 128K words of memory, a high speed printer/plotter, a 9-track magnetic tape drive and two large capacity disc drives. DEC's multiuser, multitasking operating system, RSX-11M, is used to service the processing needs of the users. User access to the host is provided by hardwired links between terminals and host time-sharing ports.

Progress in FY 80:

Three instruments were added to the network in FY 80. Instruments presently connected to the network include: Spectrophotometers; Cary 118, Perkin Elmer 580B, Cary 14; Spectropolarimeter, Cary 60; Electron spin resonance spectrometer, Varian, and a stimulus response retina experiment. The change of the host from the Honeywell 516 to the PDP 11/70 is underway.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00057-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Molecular Interactions Laboratory Data System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ramon L. Tate, Ph.D.	Computer Specialist	CSL, DCRT
OTHER:	James C. Osborne, Jr., Ph.D.	Research Chemist	MDB, NHLBI
	Arthur R. Schultz, Jr.	Processor Design Section	CSL, DCRT

COOPERATING UNITS (if any)

MDB, NHLBI

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This microcomputer (PDP 11/03) data system when fully implemented will facilitate the acquisition and processing of information from an analytical ultracentrifuge, a circular dichroic spectropolarimeter, and a laser light scattering instrument used in MDB, NHLBI to investigate the interactions between human lipoprotein subunits. Current capabilities include acquisition, display, and preprocessing of data from the ultracentrifuge and transfer of preprocessed data files to the DECsystem-10 for further analysis. The complex nonlinear analysis necessary for the characterization of interacting systems will be carried out under MLAB on the DECsystem-10. CLINK, the PDP-11/PDP-10 communications software package jointly developed by CSL and CCB, will be used to perform the data transfers. Computation of molecular weights for non-associating systems can be performed in the microcomputer. A commercially available hardware/software package for automating the laser light scattering instrument is being evaluated for possible use with the microcomputer system. Hardware is also being evaluated for performing the analog-to-digital conversion of the signal from the circular dichroic spectropolarimeter.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00058-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Californium-252 Plasma Desorption Mass Spectrometer Data System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ramon L. Tate, Ph.D.	Computer Specialist	CSL, DCRT
OTHER:	Henry M. Fales, Ph.D.	Chief	LC, NHLBI

COOPERATING UNITS (if any) LC, NHLBI
Texas A&M University Chemistry Department, Dr. Ron MacFarland

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Real-time performance and the ability to access very large data arrays in main memory are key considerations. A data system design specification that meets these requirements has been drawn up and an evaluation of available hardware and software is under way. In addition, special interface electronics that will be required are also in the initial stages of design.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00059-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Combined EDS-WDS X-ray Analysis Scanning Electron Microscope System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Ramon L. Tate, Ph.D.	Computer Specialist	CSL, DCRT
OTHER:	William A. Hagins, MD, Ph.D.	Chief, Membrane Biophysics Section	LCP, NIAMDD

COOPERATING UNITS (if any)

LCP, NIAMDD

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the development of a scanning electron microscope system capable of simultaneously analyzing the X-ray emissions of a sample under observation by both energy-dispersive and wavelength-dispersive detectors. The system permits localization and quantitation of both light and heavy elements in the sample, storage of raw and reduced data within the data system, processing of data, and transmission of data to a remote DECsystem-10 computer system at DCRT.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00060-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Measurement of Transepithelial Resistance of Kidney Tubule

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Susan Hauser	Electronics Engineer	CSL, DCRT
	Ken Spring	Staff Physiologist	LKEM, NHLBI

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microcomputer-based instrument was developed to facilitate determination of the transepithelial resistance of an in vitro preparation of kidney tubule. The instrument controls the onset, intensity, and duration of a series of electric current pulses through the preparation, and measures the resulting voltages at each end of the tubule. Presently the instrument prints the currents and voltages from which the investigator must calculate the resistances and other parameters of interest. Plans call for enhancing the instrument to perform these calculations as well.

PHS-6040
(Rev. 10-76)

Background and Objectives:

To automatically measure transepithelial resistance in vitro preparations of kidney tubule.

Significance to Biomedical Research:

Previous manual methods for making these measurements were time consuming andprone to error. With the new instrument, a complete set of measurements can be made in a few moments. Furthermore, the experiment can be re-run under the same or a different set of conditions to test repeatability or consistency of results.

Progress in FY 80:

A microcomputer-based instrument was developed to make the measurements. Results are printed on a teleprinter.

The experimenter specifies a series of electric current values (entered at the teleprinter keyboard). The instrument then applies each current in turn via a digital-to-analog converter, and measures the voltage responses at each end of the tubule via a multiplexed analog-to-digital converter. It monitors the voltages until it determines that a steady state is achieved, records the steady state response, and removes the stimulus. After all specified currents have been applied, the measured voltages are printed. At present, the investigator must calculatethe parameters of interest from these voltages and the applied currents.

Proposed Course:

Once we have more experience with the instrument in its present state, we plan to extend its capabilities to include the calculations now done by the investigator. These include: length constant, core resistance, electrical diameter, and transpithelial resistance. Of particular importance is the on-line dtermination of electrical diameter. How well this figure compares with the optical diameter is an indication of the integrity of the preparation and the validity of the other calculations.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00061-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Electron Microanalysis Facility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB, DRS
	K.E. Gorlen	Electronics Engineer	CSL, DCRT
OTHER:	L.K. Barden		CSL, DCRT
	J.S. DelPriore		CSL, DCRT
	P.S. Plexico		CSL, DCRT
	M.A. Douglas		LAS, DCRT
	E.W. Pottala		LAS, DCRT
	C.C. Gibson		BEIB, DRS
	R.D. Leapman		BEIB, DRS
	A.F. Leroy		BEIB, DRS
	C.R. Swyt		BEIB, DRS

COOPERATING UNITS (if any)

NHLBI, NIAMDD, NIMH, NINCDS

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 2.2	PROFESSIONAL: 2.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

CSL in collaboration with BEIB is developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microspy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive X-ray Spectrometry, and Wavelength-Dispersive X-ray Spectrometry.

See also: Z01 RS 10058-02
Z01 RS 10059-02
Z01 CT 00042-02

Background and Objectives:

The Computer Systems Laboratory is designing and implementing a computer systems as part of the BEIB Microanalysis Facility. The facility consists of two electron microscopes, and will be used for research into the elemental composition of biological specimens and for developing new techniques in electron microscopy.

One of the electron microscopes is a Hitachi H-700H 200 keV Scanning Transmission Electron Microscope (STEM) equipped with:

- a lithium-drifted silicon (Si(Li)) detector connected to aKevex 7000 Analytical Spectrometer for performing Energy-Dispersive X-Ray Spectrometry (EDS);
- an electron spectrometer for performing Electron Energy Loss Spectrometry (EELS); and
- detectors for forward-scattered, back-scattered, secondary, and sample electron current signals.

The other electron microscope is a Cameca 50 KeV Electron Microprobe equipped with:

- a Si(Li) detector for performing EDS;
- three Wavelength Dispersive X-rays (WDS) spectrometers; and,
- detectors for forward-scattered, back-scattered, secondary, and sample electron current signals.

A PDP-11/60 computer system is being interfaced to both microscopes to perform the following functions:

- control electron beam position, stage position, and the various detectors;
- acquire and display the spectra and image data;
- monitor and display a wide variety of "housekeeping" parameters, including: lens currents, lens temperatures, beam current, beam energy, pump temperatures, coolant flow rates, vacuum pressures, water leak detectors, floor vibrations, ambient AC fields, power supply voltages, room temperature, and room humidity.

Progress in FY 80:

This year we worked on three major aspects of data acquisition from the STEM: (1) acquisition of EELS spectral data and control of STEM beam position, (2) acquisition of EDS spectral data from the KEVEX 7000 Analytical Spectrometer, and (3) acquisition, monitoring, and display of housekeeping parameters.

EELS data acquisition and control of the STEM beam position will be done by a satellite processor connected to the PDP-11/60 by a high-speed link. The satellite was interfaced to CSL's development system, and software was written to (1) communicate with it over the high-speed link, (2) load data acquisition programs into it, and (3) aid the debugging of programs running on it. This software constitutes the basic tools required to develop data acquisition tasks for the satellite.

EDS data acquisition will be done by the KEVEX 7000, which is connected directly to the computer. Software was developed to (1) allow the programs on the 11/60 to directly communicated with and control the KEVEX 7000, (2) to save or restore spectra and associated information to or from user library files, (3) allow programs on the 11/60 to access, insert, or delete spectra contained in user library files. This software is already being used for research with the STEM.

Housekeeping parameters will be acquired by the computer by means of an Analogics AN5400 data acquisition subsystem. The AN5400 was interfaced to CSL's development system, and software was written to (1) drive the AN5400 from user programs, (2) perform AN5400 I/O from programs written in PASCAL, and (3) exercise the basic functions of the AN5400. Development of the housekeeping parameter acquisition, monitoring, and display software is just starting.

Two major pieces of equipment were ordered and will be delivered early in FY 81: (1) a color display system for displaying and processing images from the microscopes and (2) equipment for interfacing the microprobe to the computer.

Proposed Course:

Next year, we expect to:

- be able to acquire EELS and EDS spectra and images and the four electron current signals from the STEM;

- be able to display EEL and EDS images on the DeAnza display system;

- complete the housekeeping parameter acquisition, monitoring, and display software; and,

- begin work on the microprobe interface.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00062-01 CSL

PERIOD COVERED
June 1, 1980 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Metabolic Energy Measurements

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. C. Songco	Electronics Engineer	CSL, DCRT
OTHER:	R. W. Hendler	Chief, MES	LC, IR, NHLBI

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microcomputer-based instrument is being developed for the direct and indirect measurement of parameters associated with aerobic respiration. BEIB is designing an interface for a set of electrodes and CSL is developing the microcomputer and software to perform the direct measurements and the calculations needed for the indirect measurements. The system will be used to study energy transduction phenomena due to respiration in biological cell preparations.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The success of the Potentiometric Titration Controller developed by CSL and reported in previous years has led to the investigation of new areas of metabolic energy phenomena. The energy used by aerobic cells comes from controlled oxidation of ingested substances. The process uses a series of redox components arranged in order of increasing electron affinities and terminates with oxygen as the final electron. The energy released by this respiratory chain is determined by voltage characteristics of the chain and the membrane structure in which it is located.

Of interest are two electrochemical potential components: the membrane potential and the concentration gradient for protons across the membrane. Other important parameters in the process of respiration and energy transduction are the rate of oxygen uptake and the ratios of proton and other ion movements to the atom of oxygen consumed. Current methods for measuring quantities are cumbersome and time consuming. Most often, complete information about the experiment is not realized until long after the experiment has been completed.

A microcomputer-based instrument will be developed to monitor instantaneous values of these parameters as the investigator manipulates certain values by injecting additional components into the system. The device will use three electrodes to monitor the concentrations of a specific ion, of protons, and of oxygen. Algorithms, which have been developed to calculate membrane potential and the concentration gradient dynamically, will be programmed into the microcomputer software. In addition, the rate of change of oxygen, d(H+)/d(O), and d(ion)/d(O) will be calculated. The results will be displayed as analog waveforms on a six channel recorder.

Progress in FY 80:

The microcomputer hardware, consisting of an Intel single board computer with a three channel A/D converter and a six channel D/A converter has been selected. The elctrode interface is being supplied by BEIB. Programs are first designed and checked on the disk based microcomputer system which serves as the Potentiometric Titration Controller. Completed programs are down-loaded into the dedicated microcomputer to perform the experiments.

Proposed Course:

Hardware system design should be completed this year. Next year we expect the data acquisition and analysis to begin with a continuing development of software.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00063-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computer Assistance for Blind Computer Users

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Scott I. Allen	Medical Research Analyst	CSL, DCRT
	David C. Songco	Electronics Engineer	CSL, DCRT
	Perry S. Plexico	Chief, Project Development Section	CSL, DCRT
	David M. Stoffel	Computer Programmer	CSL, DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.3	PROFESSIONAL: 1.2	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the first project year a prototype computer terminal utilizing voice output communication with a blind programmer was developed. This year three low-cost improved models were placed in operation in Federal computer settings. Further studies are planned on communication needs and low cost terminal devices to aid in information processing occupations potentially open to the blind.

Background and Objectives:

This research concentrates on terminal and software requirements to assist blind programmers and other blind computer users in interacting with time-shared machines and in writing and debugging programs on independent microcomputer systems.

Methods:

A microcomputer, a $400.00 Votrax speech synthesis unit, McIlroy's English text-to-speech translation algorithm have been combined to form a voice output terminal. Pronunciation conventions are tailored to handle the full ASCII character set and computer programming contexts.

Significance to Biomedical Research:

The employability and productivity of blind programmers and blind users generally can be improved in many data processing settings. Better terminal configurations and faster data access and manipulation software are necessary tools for such improvements.

Progress in FY 80:

Three enhanced voice output modules for interfacing between a time-shared computer and a keyboard input/output terminal were developed and installed for use by blind programmers in the Federal Government. These voice output modules dramatically improved the job capability of these blind users.

Proposed Course:

Further studies will focus on interactive use of self-contained microprocessor systems by blind programmers. Also of interest are formatted CRT terminal configurations for blind specialists dealing with information storage and retrieval applications. The voice output module design will be modified for application to economical personal computer equipment costing $2,000 to $3,000.00.

Publications:

Songco, D.C., Allen, S.I., Plexico, P.S., and Morford, R.A.: How Computers Talk to the Blind: Sightless Computer Programmers Provide Input by Keyboard and are Responded to by a Synthetic Speech Unit. IEEE Spectrum, May 1980, pp. 34-38.

Allen, S.I., Songco, D.C., Plexico, P.S., and Morford, P.A.: A Voice Output Module in Use by a Blind Programmer. Journal of Visual Impairment and Blindness. 1980 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00064-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Image Processing Facility

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. L. Risso	Electronics Engineer	CSL, DCRT
	D. Syed	Chief, Systems Design Section	CSL, DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project, begun during the reporting period, is intended to provide a facility to display and analyze digital images. The project has identified a number of potential users from among those currently pursuing image processing on the campus, and from among other interested scientists in the NIH community. General specifications drawn up by CSL for such a system have been presented to these users for comments and suggestions, and after subsequent discussion, procurement of a computer-display system has been initiated.

Background and Objectives:

The objective of this project is to develop a general purpose computer facility to aid the acquisition, display, and analysis of images such as electron micrographs, CAT scans, and radiographs. This facility will be available to the NIH community.

Significance to Biomedical Research:

Study of images obtained in the biomedical laboratory is proving more and more fruitful as technology is able to supply the proper tools at a reasonable cost. Biomedical scientists are employing image analysis for a wide variety of research goals, and the use of such techniques is expected to grow very rapidly in the near future.

Progress in FY 80:

This project was initiated during the FY 80. The CSL has assembled, with the participation of an interested user community, a set of general specifications describing an image analysis facility. A detailed set of specifications for individual components has been generated, and procurement of some key parts of the system is in progress.

The system will be based on a 32 bit, 1 mega-byte computer, with a smaller 16 bit processor intended to handle image acquisition. A multi-display raster scan frame buffer will provide several users concurrent access to the central processor. Images will be digitized, if necessary, through a vidicon camera or a microdensitometer. A camera system will provide some hard copy capability.

Proposed Course:

Procurement of the outstanding components will be initiated, and during the next year development work to assemble the various parts into a working system, to adapt present software and build new program modules will begin. This project stage will require cooperation with the user community, particularly during the design phases. To this purpose, the project staff will be enlarged to include a scientist from another institute who is currently working in the image field, as well as a professional systems programmer.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00065-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Medical Information Technology Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	David C. Songco	Electronics Engineer	CSL, DCRT
OTHER:	David M. Stoffel	Computer Programmer	CSL, DCRT
	A. W. Pratt	Director	DCRT

COOPERATING UNITS (if any)
None

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves evaluating improved man-machine interface methods and identifying ways that modern microprocessor technology might benefit physicians and the practice of medicine. Interface methods that offer promise are voice input/output, bar codes (such as used with point of sale equipment), and touch screen selection systems for use with video displays. Potential applications include medical record keeping, medical education, and computer-aided diagnosis.

Background and Objectives:

The man-machine communication interface currently in use by the medical community leaves much room for improvement. This project seeks to define and develop a more human oriented interface. Our approach involves investigation and experimentation in two areas. They are the communications hardware and the communications language with associated control structure. A "communications language" consists of the allowable "sentences" or statements which comprise the dialogue of a man-machine interaction. A communications language may be described by some grammar capable of producing the allowable sentences of the language. The characteristics of the communication language used in man-machine interaction are major contributing factors to the utility of the machine. We have considered two approaches toward improved communications languages. These approaches may be described as a rule directed communication agent, and a menu driven communication interface. These two approaches simplify the interaction with computers without necessarily giving up sophistication. They are fundamentally different in their philosophies but they achieve similar goals. In the case of a rule directed agent, much knowledge of the domain of the interaction is incorporated in the system, but the user must also know the domain of the man machine communications language. In the case of the menu driven interface, the user need know very little about the interactions allowed because he is prompted every step of the way through his dialogue with the machine.

Progress in FY80:

The first part of the year was devoted to the identification, acquisition, and evaluation of a variety of communications hardware. This included two types of speech recognizer, a bar code reader, a phoneme speech synthesizer, a compact hand held terminal, and a CRT terminal with detachable keyboard. Each of these devices was evaluated to determine its suitability as a communication interface between the microcomputer and the user. The evaluation was accomplished by interfacing all of the devices to an Intel microcomputer system. An input/output handler routine was written for each device and placed under the control of a command interpreter. The devices were then used to illustrate rule directed communication. Software was written to develop a "production system" using a set of rules (a grammar) to direct the transformation of input strings to output strings.

Proposed Course:

In the next year, we will evaluate a touch sensitive panel to be used with a menu driven display. We also plan to identify a specific medical application that can benefit from the techniques we have developed. Areas under investigation include medical record keeping, computer aided diagnosis, medically oriented training, and report generation. A microcomputer system will be tailored to one or more of these applications and tested in its medical setting.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00075-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Quantitative Morphological Analysis of Cardiac Muscle Tissue

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Michael Jones	Senior Surgeon and Investigator	H IR SU, NHLBI
	Joseph Zwischenberger	Clinical Associate	H IR SU, NHLBI

COOPERATING UNITS (if any)

Clinic of Surgery, NHLBI

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Two software packages have been designed and implemented to enable interactive analysis of images of cardiac muscle tissue for the following purposes:

1. To determine percentages of myocardial fibrosis in patients with ventricular hypertrophy and in animals with experimental ventricular hypertrophy from tissues differentially stained to distinguish fibrous tissue from cardiac muscle cells.

2. To measure morphometric features of cardiac muscle tissue from photomicrographs, including cell areas, cell perimeters, capillary densities, nuclei densities, capillary spacing, percent cell areas, and percent interstitium.

Both packages are fully operational and images of specimens may be processed. We anticipate that the correlation of derived morphometric image data with other data (clinical, hemodynamic, long-term follow-up, etc.), associated with the corresponding subjects will reveal useful information underlying certain cardiac disease processes as well as providing additional useful indices for clinical decision-making.

Background and Objectives:

The objectives of this project are to provide analytic tools for making quantitative measurements of certain morphological parameters from images of light microscope magnified sections of cardiac muscle tissue. These tools apply to the following distinct areas of analysis:

1. Determinations of percentages of myocardial fibrosis in patients with congenital heart anomalies and animals with experimental ventricular hypertrophy from microscopic slides, differentially stained to distinguish fibrosis from cardial muscle cells.

2. Measurements of basic morphometric features of highly magnified cardiac muscle tissue, such as cell perimeters and areas, capillary and nuclei densities, capillary spacing, and percent cell area.

Methods Employed:

In both fibrosis quantitation and general morphometric feature determination procedures, specimens are microtomed, mounted, stained, and photographed using a high-resolution light microscope. Resultant black and white negatives are digitized by means of microdensitometry methods and entered into the Evans and Sutherland System where quantitative analysis is performed with user-interactive computer programs.

The program for determining percent fibrosis automatically removes the textured background surrounding the image of the specimen, permits "painting" of the image to remove other unwanted parts and then computes a histogram of the remaining picture element (pixels) grey scale values. Staining, photography and microdensitometry techniques were carefully experimentally optimized to yield excellent separation of pixels corresponding to collagen (fibrosis) and cardiac muscle cells. Therefore, simple dual-threshold density slicing with local neighbor analysis to resolve the small percentage of pixels lying in the ambiguous range seems to be a satisfactory approach.

The program for extracting general morphometric features permits graf-pen indication of cell contours, nuclei and capillaries. It also allows density slicing and "painting" to determine percent cell area.

Both programs offer complete control over visual rendering of images for contrast and psuedo-color control. Computer parameters are stored in a file along with other parameters associated with subjects.

Major Findings:

Developed procedures and programs are easily used. This highly quantitative approach to morphometric analysis of cardiac muscle tissue appears to show great promise as a research and clinical tool.

In the context of analyzing large numbers of images, standard microdensitometry methods are quite time-consuming.

Significance to Biomedical Research:

Prior to this work fibrosis quantitation had been accomplished by summing estimates of fibrosis in the space with a grid lattice placed over a specimen. Other morphologic measurements were made using image projection systems, planimeters, and physical painting of negatives. Our programs offer substantial improvement over previous methods.

It is anticipated that the correlation of derived morphometric image features with other known factors associated with corresponding subjects will reveal useful information about certain cardiac disease processes as well as providing additional useful indices for clinical decision-making.

Proposed Course:

Faster methods of image digitization and transmission are under investigation. Statistical package for correlating features derived from images with other features associated with the corresponding subject are under development. Images continue to be processed routinely.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00073-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cerebral Metabolic Imaging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Douglas A. Foxvog	Computer Specialist	CSL, DCRT
	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Louis Sokoloff	Chief	LCM, NIMH
	Charles F. Goochee	Computer Programmer	LCM, NIMH

COOPERATING UNITS (if any)

Laboratory of Cerebral Metabolism (LCM), NIMH

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Digitized images of autoradiographs showing cerebral metabolic activity in serial parallel microtomed sliced sections of experimental animal brains are to be enhanced, aligned, stacked, and viewed at any arbitrary cutting surface, and procedures and algorithms are to be readily transportable to an NIMH image processing system. Alignment work has begun using the Evans and Sutherland System. Initially, it is intended to use the 60^3 volume-element 3-dimensional block model software already operational on the System. The host NIMH Image Processing System has been installed.

PHS-6040
(Rev. 10-76)

Background and Objectives:

Digitized images of autoradiographs showing cerebral metabolic activity in serial, parallel microtomed sliced sections of experimental rat and monkey brains are to be enhanced, aligned, stacked, and viewed at any arbitrary cutting surface, thereby giving the investigator the ability to examine metabolic activity three-dimensionally. Procedures and algorithms are to be developed on the Evans and Sutherland System and transported to a recently installed NIMH image processing system.

Methods Employed:

To align images, outer contours of consecutive slices are automatically extracted, and one contour is automatically rotated and translated with respect to the other in order to find the alignment which produces the minimum nonoverlap area. The corresponding continuous-tone images are then aligned. After all images associated with one brain are aligned, they are stacked and displayed by means of a 60^3 volume-element three-dimensional block model developed independently for a concurrently reported project entitled "Computerized Three-Dimensional Model of the Cat's Brain Stem."

Major Findings:

The notion of examining cerebral metabolic activity three-dimensionally and our initial attempts at alignment and viewing offer great promise. In order for this concept to be practically useful, alignment procedures must be improved considerably and greater spatial resolution through data compression and/or increased on-line storage must be provided.

Proposed Course:

NIMH investigators are exploring ways of providing fixed reference points by passing rods around and/or through the specimen prior to the microtome procedure. It is expected that these reference points will permit much more accurate alignment than available with current procedures. Reference points will facilitate correction for spatial warping of images due to microtoming, mounting, audioradiography, and general handling.

Image enhancement and storage problems will be considered.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00072-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Image Analysis of Plaque Formation in Experimental Atherosclerosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	William A. Barrett	Staff Fellow	CSL, DCRT
	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Donald L. Fry	Chief	IR EA, NHLBI
OTHER:	J.F. Cornhill	M.D.	Ohio State University

COOPERATING UNITS (if any)

Laboratory of Experimental Atherosclerosis (IR EA), NHLBI

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Automated methods for quantitating plaque formation in experimental animals and its location along the arterial tree for statistical correlation with other quantitative factors such as breed, age, diet, etc. are required. Specimen preparation, image digitization, image transformation to a standard reference coordinate system and disease detection procedures are all fully operational. This method reduces processing time 300 fold over former manual methods and assures reproducibility. Resulting topographic maps describe disease in a concise and quantitative manner, providing a tool for correlation of disease patterns with local histologic, physical, and biochemical events.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The objective of this project is to provide a computerized method of accurately, reliably, and reproducibly analyzing images of stained arterial sections of experimental animals in order to quantify plaque formation as a tool for correlation of disease patterns with local histologic physical and biochemical events.

Methods Employed:

A systematized necropsy procedure and standardized format was developed for arranging and fastening the opened arterial tree to reflective panels for optical scanning and computer input. Digital images are transformed through the use of local anatomical landmarks to a standard coordinate system. An interactive edgefinding algorithm searches the image for an isopleth of maximum optical intensity transition to identify and isolate diseased areas into discrete regions forming a topographic map.

Major Findings:

It was found that this automated methodology compared favorably with previously used manual techniques while assuring reproducibility and reducing processing time by 300 fold. The maps describe extremely congruent distribution of the disease in a concise and quantitative manner and provide the researcher with a tool for correlation of disease patterns with local histogic, physical, and biochemical events. Additionally, the coordinate transformation algorithm and the edge-detection algorithm developed have applicability to several other biomedical image analysis problems.

Proposed Course:

It is intended to use the methodology developed to analyze data from several types and colonies of experimental animals and the resultant plaque data will be correlated with other relevant factors such as breed, age, diet, etc.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00074-01 CSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computerized Three-Dimensional Model of the Cat's Brain Stem

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Douglas A. Foxvog	Computer Specialist	CSL, DCRT
	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Joe Adams	Senior Staff Fellow	LND, NINCDS
OTHER:	William Livingston	Electronics Engineer	LND, NINCDS

COOPERATING UNITS (if any)

Laboratory of Neuro-otolarngology, LND, NINCDS

LAB/BRANCH

Computer Systems Laboratory

SECTION

System Design

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A three-dimensional, colored, 60^3 volume element block model representing the neuronal structure of the superior olivary complex of a cat's brain stem has been developed. The model allows rapid selection of a viewing surface computed for any selected cutting plane through the model volume. The model is intended to provide a common frame of reference for comparing anatomical and physiological data from different experimental animals. Investigators should be able to view a section of the "normal" cat on the same plane as the experimental sections and also along the plane described by various electrode penetrations in the experimental animal. The model has been developed and used successfully on the Evans and Sutherland System. Several high-precision plotters and high-resolution graphics camera stations are being investigated to achieve low-cost, publication-quality, hard copy images for reporting purposes.

Background and Objectives:

The objectives of this project are:

1. To develop and implement a three-dimensional block model of a cat's brain stem from laboratory collected data specifying cell types and their spatial relationships.

2. To provide a method for producing publication-quality colored and black-and-white two dimensional graphics that illustrate three-dimensional block model.

Methods Employed:

Consecutive 80-microthick microtomed slices for the superior olivary complex of the cat's brain stem were stained and examined by a neuroanatomist by means of a Zeiss microscope. The stage of the microscope was attached to a computer, as was a function box, thus enabling the neuroanatomist to log spatial coordinates and cell types in a computer data file. This data was transferred to the Evans and Sutherland System and used as input to the 60^3 volume element block model program specifically developed for this project. The block model software allows the investigator to view the surface of any selected cutting plane through the model volume.

Major Findings:

The model has been used successfully during the past year. It provides investigators with a more thorough understanding of the neuro-anatomy of the superior olivary complex. Also, the block software developed on this project has obvious applicability to several other biomedical imaging applications.

Proposed Course:

It is expected that the model will continue to be used and the software will be extended to other applications. Several high precision plotters and high-resolution graphic display devices are being explored in order to produce publication-quality colored two-dimensional graphics depicting selected viewing planes of the model.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00071-01 CSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Image Analysis in Automated Radiotherapy Treatment Planning

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	James M. DeLeo	Computer Systems Analyst	CSL, DCRT
	Eli Glatstein	Chief	RO, NCI
OTHER:	Douglas A. Foxvog	Computer Specialist	CSL, DCRT
	William A. Barrett	Staff Fellow	CSL, DCRT

COOPERATING UNITS (if any)
Radiation Oncology Branch (RO), NCI

LAB/BRANCH
Computer Systems Laboratory

SECTION
System Design

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is directed towards finding improved methods of analyzing computerized tomography (CT) images in order to provide optimal methods of automated radio therapy treatment planning. Various algorithms for contrast enhancement, contour detection, extraction, following, and coordinate data compression, and three-dimensional representation have been implemented and tested. Work has temporarily been suspended during the past year, pending availability of NCI radiologists for further collaboration.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The objective of this project is to find improved computerized methods for isolating specific organs and diseased areas in computerized tomography (CT) images for the purpose of improving upon computer-assisted methods of radio therapy treatment planning.

Methods Employed:

CT scans are transported by magnetic tape to the Evans and Sutherland System in the NIH Division of Computer Research and Technology (DCRT) where they are entered and analyzed. Analysis consists of applying a variety of classical and experimental algorithms for contrast enhancement, density slicing, texture analysis, contour detection, contour extraction, contour following, contour coordinate data compression, and three-dimensional reconstruction.

Significance to Biomedical Research:

Improvements in computer-assisted radio therapy treatment planning should result in improved patient care.

Proposed Course:

Work has been suspended during the past year, pending availability of NCI radiologists for further collaboration.

Projects and Activities
FY 1980
Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

LSM activities can be divided into three areas: computation, consultation, and research.

COMPUTATION

A major part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a package for the NIH community, it provides maintenance, documentation, instruction and assistance for users to interpret the results.

Statistical Packages Supported by SSS

During this year, as in the past year, the Statistical Software Section of LSM maintained the following program packages and programs:

BMD, BMDP, Biomedical Computer Programs, UCLA
SPSS, Statistical Package for the Social Sciences, SPSS, Inc.
SAS, Statistical Analysis System, SAS Institute, Inc.
P-STAT Statistical Package, P-STAT, Inc.
IMSL, International Mathematical and Statistical Libraries, IMSL, Inc.
MSTAT1, Collection of Mathematical and Statistical Programs, DCRT

During the year every package sent through at least one major update. The SSS staff answered over 4000 calls for assistance, and taught a total of eight courses on these packages; two each on the SPSS and BMDP packages and four courses on the SAS package.

The use of program packages continues to show considerable increase. The average accesses per month of all the statistical packages rose from around 12000 during FY 79 to almost 23000 in FY 80. For the fourth year in a row SAS experienced the largest increase of any of the packages. SAS averages almost 15000 accesses per month, up from 7000 per month in FY 79. The average number of accesses per month for SPSS increased from 4900 to 5500. The average combined accesses of the BMDP and BMD packages rose from 850 accesses per month in FY 79 to around 1700 this year. As an example of a package used for specialized purposes, PSTAT averaged 70 accesses per month, up from 35 average accesses per month in FY 79. The main programs and subroutines in MSTAT1 averaged 450 accesses per month, which is slightly above the usage in FY 79. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during FY 80.

MLAB Support

The Biomathematics and Computer Science Section maintains the DEC-10 interpretive program MLAB for biomathematical modeling at NIH. This package, designed and implemented by BCS staff, is used by several hundred NIH researchers each year for various modeling and graphical display tasks. It has been sent to many universities and research centers at their request, including the NIH-funded Prophet system, SUMEX-AIM at Stanford

University, and as part of the NIH-EPA Chemical Information System. The Beginner's Guide to MLAB was distributed at NIH near the end of FY 79. During FY 80, a revision (Ninth Edition) of the MLAB Reference Manual was prepared and distributed. A series of tutorial articles on MLAB in INTERFACE was begun this fiscal year: four articles have appeared to date. The DCRT course in MLAB was divided into two levels, beginner and advanced, during this fiscal year. The previous undivided course was taught during the Fall session, and the beginners' level and advanced level courses were each taught during the Spring session. MLAB was enhanced by technical improvements which increase speed of computation and reduce memory requirements. In addition, new graphics linetypes for contour maps and a new matrix operation were added.

Support of C-LAB

BCS continues support of C-LAB, a computer package for pattern recognition and cluster analysis developed by a BCS staff member. A course on C-LAB was taught during the fiscal year. Work was begun on documentation of an algorithm for determining cluster validity of data. C-LAB techniques were modified to follow the latest published methods, and compatibility with MLAB was maintained.

Support for the Unified Generator Package

This package, developed by a BCS staff member, was converted so as to be compatible with "new" WYLBUR and the EDSUTIL package of routines offered by the Computer Center Branch. As before, assistance was provided for users on request.

Support for REDUCE and PROLOG

BCS has continued support for the REDUCE system (obtained from the University of Utah) for manipulation of algebraic formulas. A DCRT course on REDUCE was taught during the Winter session. Some further documentation of REDUCE has been received, but an update of the Reference Manual in preparation at the University of Utah is long overdue. REDUCE applications contributed to several BCS research and collaboration efforts.

The PROLOG software system (obtained from the University of Edinburgh) is used for non-numerical data processing. A DCRT course on PROLOG was taught during the Winter session. PROLOG has been applied in LSM research in linguistic analysis.

CONSULTATION

Estimated percentages are:

Mathematical, statistical and computer science advice with limited computer use	5%
Mathematical or statistical advice with considerable computer use	55%
Computational advice alone	40%

Continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB have resulted in the large component of computer use in these figures.

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful, and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

The diverse nature of LSM consulting is indicated by the projects and activities listed below.

CLINICAL RESEARCH, PATIENT CARE, EPIDEMIOLOGY

Causalgia

A. Tahmoush (NICHD/LDN): Causalgia is a post-traumatic pain syndrome that has been the subject of controversy related to the issue of precise necessary and sufficient criteria for diagnosis. Work has been completed which refines the criteria using selected pain populations and the McGill pain questionnaire. A paper on this is in press in PAIN. Further work is in progress to relate the autonomic nervous system to causalgia and the outcome of treatments for relief from pain.

Multivariate Reference Regions

E. K. Harris (DCRT/LAS): Reference regions as used in clinical chemistry were studied using randomly generated M-tuples from a multivariate normal distribution with equicorrelated variables. When only one of the M tests lies outside its univariate reference range, the chances are quite huge (even with M=2) that the vector will not appear "significant." These results were not greatly affected by the size of the correlation. Other results also confirmed a "paradox" previously discussed by Healey; that is, for batteries of highly correlated tests, multivariate reference regions are likely to deemphasize positive findings in one or more of the variables judged against their separate reference ranges. This statistical result should please clinical pathologists anxious to avoid fruitless follow-up of out-of-range values in single tests.

Complications of Dialysis Study

G. Hirschman (NIAMDD): Studies were made of hospitalization rates in various categories of patients with end stage renal disease on hemodialysis. Methods for comparing rates for patients in the study differing amounts of time were devised and used. A manuscript has been prepared on this work.

Pernicious Anemia

J. Michael Poston (NHLBI/LB): Data was analyzed on the concentration of branched-chain amino-acids in serum from patients with pernicious anemia.

Longitudinal Study of Life Stresses

E. Lehr (NIA): Data organization, organization consultation in analysis, and computational assistance was provided for the analysis of stress during an aging of normal (mostly male) study group.

Guatemala-San Diego Malnutrition Study

C. Horowitz (NIMH/LDP): Programs for computation of the intra-class correlation coefficient were adapted and added to SAS. Computer assistance through SAS was provided.

Foods for Health Program

J. Pinsly (NHLBI/OPEC): The SAS system was used in the analysis of questionnaires responded to by supermarket customers. The purpose of the study was to determine the feasibility of affecting diet by supplying nutrition information in supermarkets.

Hyperthermic Cancer Therapy in Humans

Young Kim (CC/AS): Cancer patients treated by induction of hyperthermia under anesthesia, respond with attenuated hemodynamic changes compared with those reported in normal volunteers. Measured plasma catechomiamine at hyperthermic condition showed evidence of sympathetic nerve response to hyperthermia. Statistical procedures used included multiple regression analysis, anova, and descriptive statistics.

ACH and Neural Pathways

Ken Marshall (NICHD/LDN): Contingency table analyses of frequency of percent change in post-synaptic response and blood pressure were made using Fisher's exact procedures. Three pathways in the cat were studied: cerebellar, somatosensory and visual. The issue was the involvement of ACH in these pathways.

Phorbol-diester Binding

K. Baculdalal (NCI/LT): Experimental measurements were made of binding between intact cells and the tumor-producing substance phorbol-diester. LSM provided assistance in setting up MLAB procedures for computer generation of Scatchard plots.

Histogram Rescaling

M. Schlam (V. A. Hospital, Baltimore): Experimental data obtained through a flow microfluorometer is in histogram form. LSM provided an approximate method and MLAB procedures for generating a simulated histogram that would have been obtained if the same cells had been analyzed with different intensity intervals corresponding to the channels.

Electromyogram Data

I. Yaar (NINCDS/MN): The speed of muscle nerve fibers using electromyogram data collected from 20 subjects was calculated. Also, power spectra for patients before and after treatment with l-dopamine were compared. Differences were not detected.

Dialysis Analysis of Schizophrenic Patients

C. Gillin (NIMH/AP): The analysis focuses on examining the relationship of sleep patterns of schizophrenic patients undergoing dialysis treatment. Statistical analyses used include multivariate analysis of variance, and anova with repeated measures.

Sleep Analysis

W. Duncan (NIMH/AP): The analysis focuses on examining the relationship between mental illness and sleep disorders. Discriminant analysis was employed to evaluate possible contribution of sleep variables in distinguishing between groups of normal subjects, depressed (unipolar and bipolar), and insomniac patients.

LABORATORY INVESTIGATION

Molecular Structure of Hemoglobin

A. Adams (NIAMDD/LPB): Given the coordinates of the atoms of the alpha-helices in hemoglobin, the orientation of each of the axes was calculated to determine whether there is a common direction. For each helix a best-fitting line in three-dimensional space was fitted and the direction cosines of these axes were compared.

Binding Constant for Thyroid Hormone

S. Cheng (NIAMDD/CE): The binding constant of thyroid hormone and its analogs to the protein thyroxine-binding-globulin was determined. A displacement curve was calculated from data obtained in a competitive binding experiment and the binding constant was determined from the curve.

Morphology of Neurons

E. A. Neale (NICHD/LDN): A quantitative analysis of selectively stained features of identified neurons was undertaken. The range of morphologic features of neurons grown in dissociated cell culture was examined using discriminant analysis. The statistical packages used were SPSS and BMDP. A paper, with an LSM author, has been prepared for publication.

Noninvasive Measurement of Vascular Events

A. Tahmoush (NINCDS/MN): A noninvasive radiometric technique for measurement of vascular events was studied. In particular, an in vitro system was used to study the changes in backscattered light in blood flowing through an artery. The device has also been applied to blood flow in human fingertips. Statistical analyses involved the general linear model, particularly various effects of regression analysis.

Synapsis in Chick Retinas

M. Daniels (NHLBI/BG): Kolgomorov-Smirnov tests were used to study differences in synactic cleft measurements in the retina of chick embryos, at two different stages of development, with two different stains. Critical points were computed and it was possible to distinguish relevant groups.

Hepatic Fibrosis in Rabbits

A. Cheever (NIAID/LPD): Symmer's clay pipestem fibrosis was produced by Schistosoma japonicum infection in the rabbit. Gross and microscopic portal fibrosis resembled those in hepatic schistosmiasis in man. SAS analyses of statistics on surviving worm pairs, eggs laid per worm pair, etc. were performed. A paper is in press on this work.

Schistosomias in Rabbits

A. Cheever (NIAID/LPD): Quantitative parasitology was studied in rabbits injected by two strains of Schistosoma japonicum. Using SAS, the relation between worm pairs, eggs laid, and eggs in feces was studied. Striking differences in relationships for the two strains were found. Eggs of a Phillipine strain did not pass so readily to feces as did eggs of a Japanese strain. Fibrosis in organs other than the liver was minimal. A gregarious "clumping" of worm pairs was noted. Two papers are in press on this work.

Potency Analysis

J. Sullivan (NIAID/PD): Consultation of potency probit analysis associated with drug mortality studies was provided, and techniques to compare regression lines were also discussed.

NMR Spectra

M. Channing (NIAMMD/LC): Consultation and assistance were provided on using a computer program for the calculation of complex exchange-broadened NMR spectra. The program has the capability of taking explicit account of spin systems exhibiting magnetic equivalence or symmetry.

Monotonal Hybridomas

A. L. DeBlas (NHLBI/BG): Analysis of the dilution serum data for estimating the number of monotonal hybridomas after a B-lymphocyte-mycloma cell fusion.

Dental Radiography

R. Beaver (NIDR/CIB): Analysis of data in studying the impact of exposure on MTF (modulation transfer function), noise and rediographic contrast using the high sensitive screen film combination.

Pulmonary Manifestations of Collagen-vascular Disease

B. Keogh, (NHLBI/PB): The purpose of this study is to determine trends in patients with pulmonary involvement with collagen-vascular (or auto-immune) diseases. Software needed to convert and reorganize data from existing files of patient information was generated using the Unified Generator Package, supported by LSM. LSM assisted in the design of the formats for the reorganized data, the use of the generators, and in the training of users of the generated programs.

Valium-receptor Binding

T. Kushner (NIMH/BPB): Using MLAB, a differential-equation model for describing Valium, Valium-receptor binding in the presence of GABA was established.

A Calibration-type Estimator for Ultracentrifuge Data

M. Lewis (DRS/BEI): A Monte-Carlo approach was prepared to resolve the distribution of a calibration-type estimator for ultracentrifuge data.

Compartmental Analysis for Neurotransmitters

R. Brooks (NINCDS/SN): A differential-equation model for compartmental analysis for neurotransmitters was prepared using MLAB.

Pharmocokinetic Modeling

M. A. Elchisak (NIMH/ET): MLAB procedures were prepared for compartmental analysis to be used for pharmacokinetic modeling.

Chemical Kinetics

C. Patlak (NIMH): LSM helped formulate a differential equation model for chemical kinetics with an observed stimulus function (the initial infusion) driving the system.

Predator-prey

A. Venosa (EPA, Cincinnati): Helped refine a predator-prey model which has several domains of solutions. This difficulty provoked revisions in the model. The organisms were E. coli (prey) and a virus.

PROGRAM MANAGEMENT

NIH Safety and Health Survey

John R. Leach (DRS/ES): The survey purpose is to gather information about a variety of factors which directly affect the safety and health of NIH employees. The evaluation of the study will be used to improve the present safety training programs. Statistical procedures used include multivariate analysis, descriptive statistics, and frequency distributions.

Office Space Management

G. Haber (UDC for ODA): SPSS programs were developed and used to study office space occupied by male and female employees in various job classifications at NIH.

Investigator Career Profile Study

F. Harding (NHLBI/DBDR): Data on investigators associated with NIH grants have been collected to be used for program management purposes. Included are evaluation of the effects of past NIH-supported training programs, and projections of current and future training programs based upon national needs and currently available researchers. The Unified Generator Package, supported by LSM, has been used to create software for maintaining this data base and retrieving information from it. LSM provided assistance in the use of the Unified Generator Package; in the use of the generated updating, reformatting, and reporting systems; and in the training of users of the generated systems.

Text Indexing

L. Geiger (DRG/RAEB): Textual material from the IMPAC file (on NIH grants, contracts, and intramural research), the NIH Clinical Trials file, and the expertise field of the CMIS file (Committee Member Information System) was indexed or "inverted". This process provides for the preparation of thesauri giving the terms used in the texts and their frequencies of occurrence, as well as the ability to make searches based on Boolean combinations of terms with great ease and minimal cost. This makes the information contained in the textual material more accessible. The Unified Generator Package, supported by LSM, was used to create the software for the indexing process as well as for subsequent retrieval. LSM assisted in the use of this software.

MISCELLANEOUS

Computer Simulation of Neural Oscillator Populations

J. Buck (NIAMDD/LPB): Given a population of noninteracting fireflies, each of which flashes according to time signals from a pacemaker with fixed period and variance, several possible models for involvement of chance in flash synchronization were investigated. Computer models were designed that simulate chance synchrony in large and small populations as well as the persistence of synchrony in populations of rhythmically flashing fireflies. A manuscript reporting the results is in preparation.

Time Series Analysis

W. Blackwelder (NIAID/MIDP): Consultation and advice was provided on time series model fitting and forecasting by the Box-Jenkins approach. A computer program for Box-Jenkins model analysis is being developed.

Integration of a Probability Density Function

R. Simon (NCI/BR): Advice on calculating the double integral of a probability density function was provided. A multiple integration algorithm that performs an n-point Gaussian integration was implemented.

Computer Graphics for a Diffusion-reaction Surface

B. Bunow (DCRT/LAS): LSM helped construct a function, G(x,t), defining a diffusion-reaction equation solution to be graphed.

Computer Graphics for Cell Membranes

N. Gershon (DCRT/PSL): MLAB was used in drawing a simulated cell membrane surface and computing distances on this surface in order to determine rates of diffusion in the membrane.

RESEARCH AND DEVELOPMENT

BCS research included projects in computer science, biomathematics and general mathematical methods. SMS research included studies on simultaneous statistical inference and multivariate analysis. MIS research was directed towards the automated processing of medical language.

LSM research project summaries are listed below, followed by the individual project reports.

Biological and Visual Shape

H. Blum (LSM): Develops and applies a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly different levels: chromosomes, cells, organs, organisms, etc.

Discrete Mathematics and Applications

G. Hutchinson (LSM): Inclusion relations between vector spaces and related problems concerning modules over rings were studied. Preparation of scientific manuscripts by computer graphics methods using printer-plotters on minicomputers was investigated.

Non-numerical Programming Techniques and Applications

L. M. Norton (LSM): Using both general purpose and special purpose programming systems, techniques for computer processing of non-numerical data are developed and evaluated by implementing small-to-medium-scale research projects in selected application areas.

Cluster Analysis

M. B. Shapiro (LSM): Cluster analysis algorithms based on the latest published research and extensions to it were developed and tested.

Research Topics in Computer Science

G. D. Knott (LSM): Various storage and retrieval algorithms have been studied. In particular, a deletion scheme for B-trees has been developed.

Linear Methods in Statistics

J. D. Malley (LSM): Linear methods in statistics continue to be studied. Simultaneous confidence limits were obtained for ratios of means in multivariate normal populations, which extend earlier results and provide for a choice of methods applicable to several groups of data with unequal covariance matricies.

Multivariate Statistical Analysis

J. E. Mosimann (LSM): Study continued of multivariate statistical methods for the analysis of data which take the form of ratios or proportions.

Automated Data Processing of Medical Language

M. G. Pacak (LSM): The program continued for information storage and retrieval of pathology data for the Laboratory of Pathology, NCI.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00012-08 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Biological and Visual Shape

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Blum	Res. Gen. Phys. Scientist	LSM	DCRT
Other:	M. O'Connor	Mathematician	LSM	DCRT
	R. L. Webber	Chief, Clinical Invest. Branch	CIB	NIDR
	H. Hoffman	Chief, Genetics Unit	VR	DRS

COOPERATING UNITS (if any)

DCRT, NIDR, DRS

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project develops and applies a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly different levels: Chromosomes, cells, organs, organisms, etc.

Applications are to (1) automation of shape analysis for diagnosis and taxonomy, including those issuing from new devices such as the tomographic scanners, (2) the description and understanding of organ and organismic development, and (3) the psychology and neurosphysiology of shape processes in vision.

Background and Objectives:

The overall objective is to develop a formal descriptive language natural to biological shapes and apply this language to a number of problems arising in main areas of medicine and biology. This would allow for the automation of many shape processes now done by humans and permit better modeling and understanding of these processes for biological and medical purposes.

Progress in FY 80:

The methods employed stem primarily from a new geometry conceived by the principal investigator. It is based on the notion of growth as the primitive process. It is being applied to a variety of problems, both to develop new mathematics and computer science in new biologically relevant directions and to uncover and clarify biological processes taking place. The applications include cell and tissue description from light microscopy, shape description of developing cells and organs, chromosome description, visual psychophysics and visual neurophysiology.

New computer capabilities and directions have emerged from this work and continue to do so. A general program for extracting these descriptions is now available at DCRT. The program is currently being (1) rewritten to allow it to be adapted to other computers and (2) extended to allow interactive shape analysis from this description. The mathematics for extending this geometry to 3-D data, such as will be coming from the variety of new scanners, has been developed to a necessary degree. Computer programs for implementing 3-D analysis are being explored. In addition, mathematics for extracting these descriptions from gray scale data (for example, slides and X-rays) is now being developed. Computer programs for implementing these are also planned.

Extension to spherical space is being explored for application to shapes of early developing embryos.

This geometry has been applied to the study of growth and development of the human mandible. New shape invariants and growth constraints have been found. This work is being extended in two directions: (1) more thorough examination of human and extension to non-human primates, and other vertebrates, and (2) the study of genetic and environmental influences of shape development in the mouse mandible, where precise morphological studies on known genetic populations can be done.

Proposed Course:

Applications to visual system experiments at the retinal, cortical, and behavioral levels are currently being formulated for testing the visual models based on this geometry.

Publications:

Webber, R. L. and Blum, H.: Regular invariants in developing human mandibles. Science 206: 689-691, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00011-06 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Discrete Mathematics and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. Hutchinson	Research Mathematician LSM DCRT
Other:	None	

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.7	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Preparation of scientific manuscripts by computer graphics methods using printer-plotters on minicomputers was investigated.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Significance to Biomedical Research:

General purpose mathematical techniques and computer programs implementing them are made available to the biomedical research community.

Progress in FY 80:

Revision of the logical theory described in previous fiscal years was completed and accepted for publication. Studies of inclusion relations between modules over a ring (a mathematical concept generalizing vector spaces and commutative groups) continued. Most effort was directed towards proving equivalence of restricted parts of several known theories of modules over a ring, via different approaches such as modular lattices, abelian categories, and additive relation algebras and categories.

In computer science, minicomputer software was developed which generates graphical displays of scientific and mathematical text by interpretation of text files containing descriptions of the desired output. As expected, terminal display copiers have limited utility for production of scientific manuscripts. Work is continuing on the use of high resolution printer-plotters to produce hard copy of scientific manuscripts.

Proposed Course:

Study of the equivalence of different approaches to module theory will be continued. The most important unsolved problem is the classification of rings that lead to the same restricted theory of modules.

Minicomputer software to generate scientific manuscripts will be developed at least to the point that scientific and mathematical text and figures generated by the LSM graphical and modeling package MLAB can be reproduced on printer-plotters. Methods for input descriptions of the desired scientific manuscript output will be surveyed and assessed.

Publications:

Hutchinson, G.: A complete logic for n-permutable congruence lattices. Algebra Universalis, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00047-02 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Non-numerical Programming Techniques and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. M. Norton	Research Mathematician	LSM	DCRT
Other:	M. C. Pacak	Computer Systems Analyst	LSM	DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.7	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Two special purpose computer language systems for non-numerical data processing have been evaluated and made available for general use, and particular techniques appropriate for use with these systems have been developed. The systems are PROLOG (a language for logic or rule-based programming) and REDUCE (a system for symbolic algebraic manipulation). Concurrently, PROLOG has been used for research projects in computational linguistics, involving semantic analysis of English textual material at both the word level and the level of groups of sentences.

Background and Objectives:

To provide programming tools and techniques appropriate for non-numerical data processing and, concurrently, to use these tools and techniques to obtain research results in applications areas.

Significance to Biomedical Research:

The availability of these two special purpose systems, and expertise in their use, provides biomedical researchers with powerful tools with which to process research data, medical records, etc. Computational linguistics research will provide knowledge enabling more effective automated processing of textual material such as pathology reports, medical records, instructional materials, etc.

Progress in FY 80:

Two special purpose programming systems, PROLOG and REDUCE, are maintained and made available for use both by the NIH community and for selected research applications under this project. Both in the course of these applications and in consultation with users, programming techniques which make possible more effective use of PROLOG and REDUCE are discovered.

The PROLOG system, which allows one to program using conditional (or "if-then") statements in a non-procedural manner, has proven to be quite easy to use, and very appropriate for certain types of non-numerical data processing. One of these application areas is computational linguistics.

We have used PROLOG to implement routines which perform automated morphosemantic analysis of medical compound words pertaining to inflammation and surgical procedures. These routines in effect derive the meaning of compound terms from the meanings of their constituent morphemes.

On the sentence rather than the word level, PROLOG has been used as the implementation language for a program which analyzes pairs of English sentences and outputs an English sentence corresponding to a syllogistic deduction whenever one follows from the input premises. This work, successfully concluded and being prepared for publication, is a precursor of research into automated analysis of larger blocks of English text (paragraphs or groups of paragraphs). This research, in a preliminary state at present, will also involve the use of PROLOG.

REDUCE, a system for symbolic algebraic manipulation, provides a unique capability to NIH, primarily to allow "closed-form" derivations of complicated expressions and solutions of systems of equations. Unfortunately, certain factors limit its usefulness, among which are inadequate documentation and theoretical limits to the power of such a system. A major effort was made to discover (and apply via consultation with REDUCE users) effective techniques for its use. The publication of one of these techniques is pending, and another publication is being prepared which will discuss results obtained partially with the aid of the REDUCE system.

Proposed Course:

PROLOG and REDUCE will continue to be utilized when appropriate for non-numerical data processing applications. Computational linguistics research into automated processing of medical terminology at the word level and of general English text at the paragraph level will be continued.

Publications:

Norton, L. M.: A note about Laplace transform tables for computer use. SIGSAM Bulletin, in press.

Pacak, M. B., Norton, L. M., and Dunham, G. S.: Mohphosemantic analysis of -ITIS forms in medical language. Methods of Information in Medicine 19: 99-105, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00008-06 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cluster Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. B. Shapiro	Research Mathematician	LSM	DCRT
Other:	None			

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cluster analysis algorithms based on the latest published research and extensions to it were developed and tested.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The main objective is the development of computer programs and methods for cluster analysis and related problem areas for use by NIH researchers.

Significance to Biomedical Research:

Pattern recognition techniques are now being widely used on biomedical data for classifying objects, for finding relationships between variables, and for processing biological images. These applications of artificial intelligence have led to both automatic processing and a better understanding of data.

Progress in FY 80:

Cluster analysis and related work has been in three areas:

1. The development and testing of cluster analysis algorithms based on the latest published research and extensions to it.

2. A study of algorithms for determining cluster validity of data is continuing.

3. A statistical and cluster analysis of enzymes found in blood serum. Data from 79 normal subjects was used to determine the number of enzymes present (22), whether the data clustered by families (it did), and whether there was a typical pattern found (there was not). Work continues with an analysis of similar data collected from cancer patients during the course of treatment. Hopefully, the presence or absence of specific enzymes will be linked with specific treatments or periods of health.

Proposed Course:

A wider range of cluster analysis algorithms will continue to be developed and applied.

Publications:

Lieblich, A. K., Symmes, D., Newman, J. D., and Shapiro, M. B.: Development of the isolation peep in laboratory bred squirrel monkeys. Animal Behavior 28: 1-9, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00009-06 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Research Topics in Computer Science

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. D. Knott Computer Specialist LSM DCRT
Other: None

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, since such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, a study of the B-Tree method of storage and retrieval methods is underway. This has resulted in the development of a method to delete items from a B-tree in efficient manner.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve the use of computing in biomedical computation.

Progress in FY 79:

The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Concurrently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree methods. Various improvements and refinements in both the algorithms and their analysis are being studied.

Most effort has gone into studying the B-Tree data structure for large files and developing a deletion algorithm to efficiently remove items from B-Trees.

A paper describing routines to manage an extendible array file which underlies most storage and retrieval methods has been prepared for publication.

Publications:

Knott, G. D.: MLAB - A mathematical modeling tool. Computer Programs in Biomedicine 10: 271-280, 1979.

Knott, G. D.: Procedures for managing extendible array files. Software Practice and Experience, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00039-03 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Linear Methods in Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. D. Malley	Research Mathematician	LSM	DCRT
Other:	None			

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Statistical Methodology Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Linear methods in statistics continue to be studied. Simultaneous confidence limits were obtained for ratios of means in multivariate normal populations, which entend earlier results and provide for a choice of methods applicable to several groups of data with unequal covariance matrices. These completely generalize previous procedures.

Further, the study of multiple comparison of ratios was extended to non-normal data, in particular data having exponential, gamma and Weibull distributions. These are commonly used to study survival and lifetime data, and the new methods allow comparisons among several groups of the model parameters.

Progress in FY 80:

The overall objective of this project is the study of linear methods in statistical analyses. During the past year, in addition to family confidence limits for ratios of normal and non-normal means, and work in automorphism groups and algebras, the linear methods were utilized in the study of log linear models for contingency tables.

Publications:

Mosimann, J. E. and Malley, J. D.: Size and Shape Variables. In Multivariate Methods in Ecological Work. Orloci, L., Rao, C. R., and Stiteler, W. M. (Eds.). Fairland, Maryland, International Co-operative Publishing House, 1979, pp.175-189.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00013-06 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Multivariate Statistical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. E. Mosimann	Chief, LSM	LSM	DCRT
Other:	M. V. Ratnaparkhi	Visiting Associate	LSM	DCRT
	J. D. Malley	Research Mathematician	LSM	DCRT
	J. N. Darroch	Flinders University, Australia		
	I. R. James	University of Western Australia, Nedlands, Australia		

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The overall objective of this project is the study of multivariate statistical methods for the analysis of data which take the form of ratios or proportions.

Study continues on multivariate statistical methods (size-shape methods) for analyzing ratios following a multivariate lognormal distribution. Studies also continue on ratios which follow an Inverted Dirichlet distribution. One publication with Ian James in the latter area appeared this past year. In this study characteristic properties of both the Dirichlet and lognormal distributions were noted. Studies on principal component and canonical analyses for size and shape variables (with J. N. Darroch) were undertaken. The Principal Investigator presented a review paper of his work at the NATO Study Institute on Statistical Distributions in scientific work at Trieste, Italy. The PI was also a scientific director of that Institute. A study on bivariate distributions where the conditional distribution of Y given X is a Beta distribution (with M. V. Ratnaparkhi) was completed.

Publications:

James, I. R. and Mosimann, J. E.: A new characterization of the Dirichlet distribution through neutrality. Annals of Statistics 8: 183-189, 1980.

Taillie, C., Ord, J. K., Mosimann, J. E. and Patil, G. P.: Change Mechanisms Underlying Multivariate Distributions. Ord, J. K., Patil, G. P., and Taillie, C. (Eds.): Statistical Distributions in Ecological Work. Fairland, Maryland, International Co-operative Publishing House, 1979, pp. 157-191.

Mosimann, J. E. and Malley, J. D.: Size and Shape Variables. In Multivariate Methods in Ecological Work. Orloci, L., Rao, C. R., and Stiteler, W. M. (Eds.). Fairland, Maryland, International Co-operative Publishing House, 1979, pp.175-189.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT 00001-09 LSM

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Data Processing of Medical Language

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. G. Pacak	Computer Systems Analyst	LSM	DCRT
	A. W. Pratt	Director		DCRT
Other:	G. Dunham	Computer Programmer	LSM	DCRT
	S. Harper	Computer Programmer	LSM	DCRT
	I. Garcia-Hidalgo	Guest Worker	LSM	DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Medical Information Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major objective of the project is the continuation of the program for information storage and retrieval of pathology data for the Laboratory of Pathology, NCI. The entire corpus of surgical pathology will be encoded.

Work continued on the development of a generalized system for automated morphosemantic segmentation and paraphrasing algorithm of medical compound words derived from Greek and Latin.

Progress in FY 80:

In June, 1979 the Medical Information Science Section renewed collaboration with the Laboratory of Pathology, NCI. This Laboratory plans to encode its entire corpus of surgical pathology diagnoses since 1953. Lexical studies and revisions, both for retrieval accuracy and linguistic completeness were accomplished in collaboration with Dr. D. Henson of NCI. MIS collaborated in the design of a data base for the Laboratory of Pathology which will become part of the Clinical Information Utility data base research tool for the NIH Clinical Center.

MIS also began work on the creation of a lexicographic data base which will contain linguistic, semantic and definitional information which could be used for the construction of special purpose medical microglossaries.

During FY 80 MIS undertook a short term project examining the potential of automatic translation of medical nomenclatures from English to Spanish using the tumor nomenclature (International Classification of Diseases for Oncology, 1400 terms) in both English and Spanish versions. It was found that a simple syntactic transformation algorithm and associated set of morphological rules can be used for translation with a satisfactory degree of accuracy.

In addition MIS constructed a stem dictionary for the "viral hepatitis" data base which was produced by the National Library of Medicine. This hepatitis data base consists of 5,500 lexical entries, the number of which will be reduced to about 2,000 stem entries. However, it was found that a large number of medical terms in the "hepatitis" data base are not listed in SNOP or SNOMED or in Dorland's and Stedman's medical dictionaries. Semantic assignment for the stem entries will be made in cooperation with medical experts in the field of liver diseases.

Work was accomplished on automated morphosemantic analysis and paraphrasing of medical terms derived from Greek and Latin. Also, an experimental comparative study was made of medical compounds in English, French, Italian, Spanish, and German.

MIS extensively tested a computer program which produces paraphrases of -ITIS forms via morphosemantic analysis. Results were sufficiently encouraging to warrant the application of the same methodology to the analysis of terms pertaining to -STOMY, surgical procedures, in particular forms ending in -TOMY, -ECTOMY, and -RRHAPHY. This involved the identification of morphosemantic distribution patterns in such forms, the development of paraphrasing rules on these patterns, and the incorporation of this information into computer programs. Results continued to be very promising, supporting the goal of developing a generalized system for automatic analysis of medical compound words. Such a system could be adapted for use with medical languages other than English as mentioned before.

During this past year MIS has expanded the use of PROLOG, a high-level programming language which is very well suited for research in computational linguistics.

During FY 80 MIS updated tape copies of computer-oriented medical dictionaries (SNOP, ICDO) and made them available to two medical schools and two foreign research groups.

Publications:

Pacak, M. B., Norton, L. M., and Dunham, G. S.: Morphosemantic analysis of -ITIS forms in medical language. Methods of Information in Medicine 19: 99-105, 1980.

Dunham, G. S., Pacak, M. G., Epstein, M.: Linguistic techniques for utilizing the medical record. Proceedings of the ASIS Annual Meeting 16: 358, 1979.

Research Projects
FY 1980
Laboratory of Applied Studies

Eugene K. Harris, Chief

Computer-aided analysis of electrocardiograms. J. Bailey, M. Horton (LAS); cardiologists and biomedical engineers in U.S.A. and abroad. To evaluate the utility of leading computer programs for ECG interpretation, and to search for optimal computer-based methods of extracting medically significant ECG patterns. The method of using interleaved digital samplings from the same analog tracing to test reproducibility was applied to Version 2 of the IBM program with and without the comparison option. A report comparing two ECG programs (IBM and GRI) using documented data from 300 patients at the Glasgow Royal Infirmary is now awaiting publication.

Computer systems for diagnostic imaging: J. Bailey, M. Douglas, B. Line (CC, Nuclear Medicine); H. Ostrow (CSL); M. Green, et al. CC, Nuclear Medicine). Development and application of computer systems to such diagnostic imaging activities as ECG-gated radionuclide angiocardiography, functional mapping, and other scintigraphic studies of kidney, brain, heart, and lung.
A major development has been the recent acquisition of a DeAnza image processing system and the development of PICTUR, a software package which enables interactive manipulation and analysis of images. This system has been successfully applied in cardiac scintigrams to determine edges and background and to superimpose blood pool and myocardial perfusion images.
A second development has been the use of functional mapping of renal scintigraphic data to reveal renal artery stenosis, surgically induced in dogs.

Computer-based studies in pulmonary pathophysiology and respiratory disease. J. Bailey, T. Stibolt and others (LAS); R. Crystal, A. Nienhuis, B. Keogh (NHLBI); A. Jones (CC, Diagnostic Imaging). To achieve better understanding of pulmonary pathophysiology through use of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of predictions with real patient data. A computer-based technique was developed to determine relative amounts of elastic versus resistive work in breathing and has been applied to sixty patients. Another computer-based method was developed for analyzing gas exchange parameters on a breath-by-breath basis in patients during non-steady state exercise.

Computer-based studies in ultrasonography. T. Stibolt, M. Douglas, J. Bailey (LAS); B. Maron, J. Gottdiener (NHLBI); S. Leighton (DRS, BEIB). Development of computer systems for image enhancement and three-dimensional reconstruction from ultrasound data, particularly data derived from scanning of heart and intra-abdominal organs. Attempt was made to construct three-dimensional models of the heart from planar scans produced by the Varian Sector Scanner, angled at 2 degree intervals. These models revealed a previously unappreciated limitation imposed by the position of the heart with respect to the ribs resulting in inadequate visualization of the septum and only 17-22% of the left ventricle.

Statistical research in clinical pathology. E. Harris, M. Horton (LAS); G. Shakarji (DMB); clinical chemists in U.S.A., Europe, and Japan. Application of variance component and time series analyses to description of reference distributions of clinical laboratory tests, to serial studies of normal biochemistries, and to the design of criteria for recommended precision and accuracy of analytic methods. Reports of applications of time series analysis to a large-scale health monitoring program in San Francisco, and to data from England on the significance on short-term biochemical changes were published during FY 80. Comparative studies of univariate and multivariate time series models were initiated, using both real and simulated data.

LABORATORY INVESTIGATION

Mathematical modeling of biological processes. J. Fletcher (LAS); A. Spector (University of Iowa); R. Schubert (Louisiana Tech. University). Development and application of mathematical models in studies of substrate transport in the microcirculation, in diffusion processes in physiology, and in macromolecule-ligand binding equilibria. A theoretical analysis of the probable role of myoglobin in facilitating oxygen diffusion in muscle tissue has been completed and published. Modeling and experimental work on microcirculatory processes in the autoregulation of oxygen supply within an organ is currently underway.

Mechanisms of active transport/biochemical kinetics. B. Bunow (LAS); A. Kaplan (NCI); J. De Simone,et al. (Medical College of Virginia). Experimental and mathematical studies of the energy mechanisms for active transport and of multi-state biochemical kinetics in cells and membranes. Theoretical studies this year have revealed the insufficiency of current, widely accepted methods and hypotheses to explain the energizing or localizing of active transport mechanisms. Collaborative work has begun on the energetics of transport and metabolism in various tissues.

Hybrid computing to analyze physiologic signals and construct simulation models. E. Pottala, A. Mitz (LAS); various NIH scientists. Using LAS minicomputer system (MAC-16) for hardware simulation of physiologic functions and for analysis of analog signals (myogram, ultrasonogram, etc.). An operating system has been developed for the MAC-16 system which provides users with easy access to compilers and major programs, handles I/O for all peripherals, and allocates system facilities and storage during execution of user programs. Additional programs were developed for preliminary A/D conversion and display of ECGs from rats with acute, experimental cardiotoxicity. EMGs from patients of the Medical Neurology Branch, NINCDS are also being analyzed with this system.

Image processing in electron-loss spectroscopy. E. Pottala, M. Douglas (LAS); K. Gorlen (CSL); J. Costa (NIMH); C. Fiori (DDR, BEIB), et al. Development and implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron-loss and X-ray spectra indicating the location of extremely small quantities of important chemical elements and the active protein molecules within cells. Image processing capabilities have been developed on the recently acquired DeAnza system (see also Nuclear Medicine) and used to determine fluorine distributions in electron micrographs of salivary glands.

COMPUTER RESEARCH AND DEVELOPMENT

Mathematical and computational methods for non-linear equations. R. Shrager, J. Fletcher (LAS); R. Hendler (NHLBI); A. Schechter (NIAMDD). Study of methods of fitting non-linear models and mathematical methods of spectral analysis. Currently under development is a decomposition procedure for the analysis of the spectra of mixtures of chemical reactants to determine individual physico-chemical characteristics and reactive mechanisms.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems. M. Bieterman, J. Fletcher, B. Bunow (LAS); I. Babuska (University of Maryland). Study, development, and implementation of efficient, flexible numerical methods for the solution of nonlinear ordinary and partial differential equations involved in modeling dynamic physiological processes. Research and testing continued during FY 80 on the use of finite element numerical methods for the solution of time-dependent reaction-diffusion equations. Validation of finite element computer programs has been completed, while mathematical theory has been developed for the adaptive solution of coupled systems of kinetic equations.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00002-10 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980.

TITLE OF PROJECT (80 characters or less)

Computer Aided Analysis of Electrocardiograms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief, MAS	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
OTHERS:	S. Allen	Medical Research Analyst	CSL	DCRT
	M.E. Womble, Aeromedical Cybernetics Branch, Brooks AFB, Texas			
	P. MacFarlane, Medical Cardiology, Glasgow Royal Infirmary, Scotland			
	D. Savage	Framingham Heart Study		NHLBI
	E.K. Harris	Chief	LAS	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.

PHS-6040
(Rev. 10-76)

Background and Objectives:

In the past fifteen years numerous computer programs implemented upon a variety of computer systems have been developed for analysis of routine ECG's. Computer processing of ECG's has become a sizeable enterprise in many parts of the country, including both commercial bureaus offering service for a fee and non-commercial (academic or government) centers establishing the capability for themselves. Recently the Tri-Services Medical Information Systems (TRIMIS) Bureau of the Department of Defense has implemented a network of ECG processing centers to serve the entire Armed Forces.

Since 1970, LAS in collaboration with the NHLBI Cardiology Branch, has studied several ECG analysis programs to determine which, if any, would be useful to implement on the NIH campus. As a result of this work, an evaluation methodology was evolved which was published in 1974 and has become one of the standard references in the field. Although a program was selected and implemented in 1974 for daily use at NIH, additional programs and other computer systems continue to be evaluated as possible improvements to the NIH system with regard to cost and accuracy. Past evaluations have included the ECAN-D program (1964), the Mayo-IBM program (1968), the experimental IBM program (1971), AVA 3.4 (Pipberger) program (1975), ECAN-E (1976), and IBM Version 2 (1977). Guidelines for evaluation of ECG programs which were developed by LAS have been adopted by the American College of Cardiology. LAS also provided consultation to TRIMIS concerning functional specifications for its ECG processing systems.

Progress during FY 80:

A method, published in 1974 for using interleaved digital samplings from the same analog tracing to test reproducibility of programs has been extended and applied to Version 2 of the IBM program (1976) (Reference 1). This method has recently been adopted by the European Communities Project for Common Standards in quantitative Electrocardiography (CSE). LAS has also continued to develop general guidelines for the evaluation of ECG programs (References 2-5).

A series of 300 ECG's were collected on patients in the Glasgow Royal Infirmary, (GRI), Scotland. Clinical documentation of the patient's cardiovascular status by non-ECG means in the form of enzyme studies, cardiac catheter laboratory data, etc., was obtained whenever such investigations were warranted, i.e., in most cases. The standard 12 lead ECG data was analyzed by the IBM program at NIH; the modified McFee lead (XYZ) ECG data was analyzed by a program developed at GRI. The results of these two programs were compared with respect to accuracy where clinical documentation existed and with respect to cardiologist agreement in all other cases (Reference 6).

Members of LAS and CSL developed specifications for a minicomputer system to be dedicated to ECG analysis which the Clinical Center plans to procure. LAS and CSL are currently evaluating vendor proposals.

The Framingham Heart Study proposes longitudinal studies of routine ECGs in that population. LAS has supplied the data collection cart and means for computer processing.

Significance:

The estimated number of computer-processed ECG's in North America was 600,000 in 1971 and 6,300,000 in 1978. In view of this increase in computer usage, it will become even more important to have methodologies and guidelines by which ECG computer systems can be evaluated.

These studies seek to establish the diagnostic limits of the ECG itself and the degree to which computerized algorithms may achieve these limits. Important evaluation methodology, which may have a significant impact on the further diffusion of computer technology in electrocardiography, continues to be developed. Furthermore, the epidemiologic significance of the routine ECG (i.e., its usefulness in detecting disease within a community) may be even greater than that suggested by its limited diagnostic power; if that is true, as some authorities have suggested, then computer processing may allow this significance to be appreciated.

Proposed Course:

Testing of ECG programs developed by other organizations was largely completed in FY 79. LAS does not anticipate further evaluation of ECG programs unless a significant innovation in technology occurs. One such innovation would be the acquisition and use of 12 or 15 leads simultaneously. Another such innovation would be sophisticated computer-based feature extraction schemes.

Meanwhile LAS proposes to study the epidemiologic significance of the routine ECG in collaboration with the investigators of the Framingham Heart Study. The ECG correlates of heart diseases such as coronary disease, mitral prolapse, and asymmetric septal hypertrophy in a free-living population are of particular interest.

Publications and Abstracts:

1. Bailey, J.J., Horton, M.R.: Reproducibility of version 2 of the IBM program with and without the serial comparison option. In Macfarlane, P.W. (Ed.): PROGRESS IN ELECTROCARDIOLOGY. Focal Press Inc., New York, 1979, pp. 259-263.

2. Bailey, J.J.: The use of cardiac scintigraphy for documentation of type A ECG diagnostic statements. In Pryor, T.A., and Bailey, J.J. (Eds.): COMPUTERIZED INTERPRETATION OF THE ECG, IV. Engineering Foundation Publication #79-01, United Engineering Center, 345 East 47th Street, New York, 1979, pp. 185-197.

3. Bailey, J.J., and Horton, M.R.: Type A electrocardiogram data bases: Purpose and development. In Wolf, H.K., and Macfarlane, P.W. (Eds.): OPTIMIZATION OF COMPUTER-ECG PROCESSING. (in press).

4. Bailey, J.J., Harris, E.K.: Evaluation of ECG interpretation: truth versus beauty. Proceedings of the 1980 Engineering Foundation Conference: COMPUTERIZED INTERPRETATION OF THE ECG, V. (in press 1980).

5. Bailey, J.J.: The future of gold standards and computerized electrocardiography. Proceedings of the 1980 Engineering Foundation Conference: COMPUTERIZED INTERPRETATION OF THE ECG, V. (in press 1980).

6. Macfarlane, P.W., Melville, D.I., Horton, M.R., and Bailey J.J.: Comparative evaluation of the IBM (12 lead) and Glasgow Royal Infirmary (3 orthogonal lead) ECG computer programs. Circulation (in press 1980).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00003-09 LAS

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computer Systems for Nuclear Medicine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief, Med. Appl. Sec	LAS	DCRT
	M.V. Green	Ch, Appl. Physics Sec	NM	CC
	M.A. Douglas	Comp. Syst Analyst	LAS	DCRT
	T.B. Stibolt, Jr.	Senior Staff Fellow	LAS	DCRT
OTHERS:	H.G. Ostrow	Engineer	CSL	DCRT
	S.L. Bacharach	Physicist	NM	CC
	A.E. Jones	Chief, Diagnostic Imaging	NM	CC
	G.S. Johnston	Chief	NM	CC
	B.R. Line	Staff Physician	NM	CC

COOPERATING UNITS (if any)

Nuclear Medicine Department, CC, NIH
Computer Systems Laboratory, DCRT, NIH

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.1	3.0	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.

Background and Objectives:

Since FY 72 LAS and CSL in collaboration with the Nuclear Medicine Department, CC have been involved in the acquisition and development of several minicomputer systems which gather and process data from the scintillation cameras in the Nuclear Medicine Department.

The objective of this program is continuing development of computer based algorithms, which have already found wide-ranging applications, including: fitting mathematical models; mapping the parameters of such models over time and in different regions of an organ; image processing; interpolation, expansion, and contraction of image arrays; and pattern recognition.

Progress during FY 80:

Continued additions have been made to IMAGE 7 PSTACK which are general purpose, interactive, DEC-10 based, image processing packages capable of accepting data from a variety of sources, such as the nuclear medicine minicomputer system.

The LAS DeAnza image processing system has been installed and extensive software has been written for it. An interactive package of software, PICTUR, has been developed. PICTUR currently includes among its options: panning, zooming, regular and irregular region of interest definition, histogram formation, profile formation, color and grey level table manipulations, file arithmetic, edge detection operators, movie display, background subtraction, normalization, and, for electron-microscopy, dense body calculations.

The DeAnza based image processing system has been used to compute histograms of left ventricular difference images and to display paired left ventricular thallium and blood pool movies. While the main thrust of IMAGE, PSTACK, and the DeAnza terminal has been towards processing dynamic scintigraphic images, it has found ready application in electron-microscopy images (see project report on electron-microscopy). Cameras have been acquired to take publication quality pictures from the DeAnza display.

Analytical methods developed in FY 77-79 were used to determine a close relationship between blood flow as measured by an electromagnetic flowmeter and cardiac function as determined by scintigraphy in Baboon preparations (Reference 1).

Previous work in FY 76 showed a significant enhancement of radionuclide renography by the use of functional maps and since FY 77 functional maps have come into routine clinical use in the Nuclear Medicine Department. A series of five dogs was studied before and after surgical ligation of a segmental renal artery. Using the functional mapping techniques, it was possible in three dogs to demonstrate the presence of a defect. Defects were not detected in any dog with contrast angiography, the current definitive technique. This work was presented at the Society of Nuclear Medicine Meeting in June (References 2 & 3).

LAS in collaboration with Nuclear Medicine and Pulmonary Branch proposed to investigate the reproducibility of pulmonary scintigraphy and its correlation to pulmonary functions in a series of normal patients. The protocol for the normal population was approved by the Clinical Center in FY 79. However, technical difficulties in the Pulmonary Branch have resulted in a temporary deferment of this study.

Significance:

Scintigraphy is a noninvasive tool which shows considerable detail concerning the dynamic function of an organ on a regional basis. Computer processing not only enhances scintillation images but allows quantification of the dynamic function. Real time implementation of algorithms on the minicomputers allows the clinical investigator to perform repeated studies on patients with exercise or therapeutic manipulation, thus better elucidating the nature of the patient's pathophysiology.

Proposed Course:

A magnetic tape drive has been ordered to facilitate data interchange for the LAS DeAnza system and disk drive has been ordered to improve storage capabilities. Further studies of the combined use of myocardial (thallium) images and blood pool images to refine detection of regional wall motion and perfusion and to determine "absolute" volumes, if possible, are planned. Methods for enhancing dynamic myocardial images will be extensively investigated, using IMAGE, PSTACK, and the DeAnza terminal. A proposed project is to obtain an improved estimate of ejection fraction by refined automatic delineation of the end-systolic left ventricle.

With the cooperation of the Hypertension-Endocrine Branch (NHLBI), renal scintigraphy with functional mapping will be applied to a series of hypertensive patients suspected of having segmental renal arterial disease. These patients are to be treated with a new drug that has demonstrated the potential of producing local renal arterial dilatation. Additionally, some of these patients may undergo renal artery dilatation using a newly developed catheter technique. Functional mapping will be used in evaluation and follow-up of both patient groups. This study is currently awaiting approval of I-123 iodohippuran as a diagnostic radionuclide by FDA.

Publications and Abstracts:

1. Green, M.V., Ostrow, H G., Scott, R.N., Douglas, M.A., Bailey, J.J., Johnston, G.S.: A comparision of simultaneous measurements

of systolic function in the baboon by the electromagnetic flowmeter and high frame rate, ECG-gated blood pool scintigraphy. Circulation 60(2):312, 1979.

2. Stibolt, T.B., and Bradley-Moore, P.R.: Renal functional mapping to detect segmental arterial lesions. Journal of Nuclear Medicine 20(6):657, 1979.

3. Stibolt, T.B.: Functional Mapping in the evaluation of renal scintigraphic studies. COMPSAC Proceedings 79. IEEE #236, 79CH 1470-5, 1979, pp. 660-665.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00034-04 LAS

PERIOD COVERED
October 1 1979 to September 30 1980

TITLE OF PROJECT (80 characters or less)
Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief MAS	LAS	DCRT
	B.J. Bunow	Senior Staff Fellow	LAS	DCRT
	B.R. Line	Staff Physician	NM	CC
	T.B. Stibolt	Senior Staff Fellow	LAS	DCRT
	R.G. Crystal	Chief	PB	NHLBI
	A.W. Nienhuis	Chief	CHB	NHLBI
OTHERS:	J.E. Fletcher	Chief, AMS	LAS	DCRT
	E.K. Harris	Chief	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	B.A. Keogh	Visiting Scientist	PB	NHLBI
	A.E. Jones	Chief, Diagnostic Imaging	NM	CC
	B.D. McLees	Chief, Critical Care Unit		CC

COOPERATING UNITS (if any)
Nuclear Medicine Dept., CC, Pulmonary Branch NHLBI, Clinical Hematology Branch, NHLBI Critical Care Unit, CC

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section. Medical Applications Section

INSTITUTE AND LOCATION
DCRT NIH Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2 0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves a collaborative effort of LAS with the Nuclear Medicine Department CC; the Pulmonary and Clinical Hematology Branches, NHLBI; and the Medical Intensive Care Unit, CC. It is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of model predictions with real patient data.

Background and Objectives

Numerous attempts have been made in the past to quantify pulmonary function. Inhomogeneities in the lung required certain simplifying assumptions to be made which tended to obscure the true nature of lung function. Furthermore, certain nonlinearities inherent in the lung system allowed only partial quantitative models and sometimes these could only be expressed in the form of nomograms of graphs.

Within recent years it has been possible to apply computer technology to numerous diagnostic tools, viz, spirometry, dynamic compliance studies, multiple inert gas studies, pulmonary scintigraphy, cardia catheter studies, and blood gas studies.

This program involves the Pulmonary and the Clinical Hematology Branches, NHLBI; the Medical Intensive Care unit, CC; the Nuclear Medicine Department, CC; and the Laboratory of Applied Studies, DCRT. The objectives include the use of computer technology to refine diagnostic methods and to construct models for pulmonary gas exchange and respiratory mechanics.

Progress in FY 80:

A computer based technique has been developed to extract the work done on the lungs during normal respiration and at increased respiration rates. This technique allows comparison of the total work required for ventilation as well as dissection of components related to airway resistance and elastic forces among groups of patients with various disease processes. The technique has been applied to more than sixty patients allowing quantitation of these parameters. The study has begun to provide a quantitative basis for certain widely accepted concepts, not previously quantitated, viz, that work of breathing is increased due to increased airway resistance in emphysema whereas in restrictive lung disease it is increased due to decreased elasticity.

In collaboration with the Clinical Hematology and Pulmonary Branches, LAS has set up an inexpensive system for breath by breath analysis of gas exchange parameters during non-steady state exercise. This system allows measurement of the overall system response (lungs, heart, blood, and muscle) to exercise. In particular it can be used to detect anaerobic threshold, i.e., the point during exercise at which sufficient oxygen is no longer delivered to exercising muscles.

Significance:

In certain diseases of lungs, blood (e.g. hemoglobinopathy), and cardiovascular system, the assessment of the patient's condition at various points in the course of disease may be no better than a subjective impression given by the patient, his family, or his physician. An alternative method of assessment which could be more objective involves the use of continuous exercise; one can evaluate the overall ability of the patient to meet the demands of exercise by monitoring his ECG, blood pressure, blood gases and lactate, oxygen consumption, etc., in a reliable and reproducible manner. The detection of "anaerobic threshold" may be of particular clinical importance when considering response to therapy or disease progression.

The sensation of "shortness of breath" is currently poorly understood. This phenomenon clearly has components of neural as well as clinical origin. Both the work of breathing and non-steady state exercise measurements should give additional insight into the origin of this complaint in patients with various disease processes. Additionally, prognostic and therapeutic decisions might be more appropriately made when this data is used in conjunction with other parameters.

Proposed Course:

Continued measurement of the work of breathing in patients studied by Pulmonary Branch will continue. Criteria from these tests of diagnostic or therapeutic usefulness will be established in the patient population. During FY 81, it is expected that this test will be fully automated using a small digital computer in the pulmonary function lab.

Studies of non-steady state exercise in both normal patients and patients with Idiopathic Pulmonary Fibrosis are in progress. The effects of short term training, supplemental oxygen during exercise, disease progression and therapeutic intervention are being investigated. In addition, effects of transfusion on exercise parameters are being studied in patients from the Clinical Hematology Branch.

Publications and Abstracts:

Keogh, B.A., Stibolt, T.B., Price, D.W., Line, B.R., and Crystal, R.G.: Work of breathing in pulmonary sarcoidosis: A monitor of parenchymal disease. Am. Rev. Respir. Dis. 121:4, Supplement p. 155, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00043-02 LAS

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Title: Computer-based studies in ultrasonography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.B. Stibolt. Jr.	LAS DCRT
	B.J. Maron	CB NHLBI
OTHERS:	M.A. Douglas	LAS DCRT
	J.J. Bailey	LAS DCRT
	S.B. Leighton	BEIB DRR

COOPERATING UNITS (if any)

Radiology	CC
CB	NHLBI

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	1.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves collaboration of LAS with the Cardiology Branch, NHLBI; the Diagnostic Radiology Department, CC; and Biomedical Engineering and Instrumentation Branch, DRR. It is directed toward computer-based processing for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data. The principal sources of data are wide-angle, phased array echo-cardiography B-mode, gray scale, abdominal ultrasonography.

PHS-6040
(Rev. 10-76)

Background and Objectives

Ultrasonography allows non-invasive visualization of many organs without the hazard of ionizing radiation. Due to its safe nature and little or no patient discomfort, it is an excellent tool for screening and multiple repeat follow-up studies. Unfortunately, certain limitations relating to presence of bone which is completely opaque to sound waves and to processing practices make this technique fall short of its full potential. Using the computer, it is possible to overcome or circumvent many of these limitations.

Progress in FY 80:

Using the Varian Sector scanner acquired by Cardiology Branch and an NIH designed support device, serial images of two patients' hearts were obtained. The images represented planes angled at intervals of two degrees. These images were used to construct image models of the two patients' left ventricular walls and septa. These models revealed a previously unappreciated limitation of the sector scanning technique when applied to the heart. It was found that, due to constraints imposed by the location of ribs and the position of the heart in the medinstinum, inadequate visualization of septal structures is a common problem. This problem is subtle as the planar images give no indication of the disparity between anterior and posterior structures visualized.

Significance:

Patients with hypertrophic cardiomyopathy are at increased risk of sudden death. Unfortunately, many of these persons are not diagnosed ante-mortum because they are asymptomatic. A reliable technique to screen those persons with a family history of hypertrophic cardiomyopathy would be of great use since prophylactic drug therapy is probably feasible. Unfortunately, many different patterns of hypertrophy appear to exist in the population afflicted. Techniques to assess the distribution of hypertrophy are needed in those patients with uncommon distributions, especially those missed by traditional M-mode echocardiographic techniques. Additionally, it is likely that the prognosis may differ among the various patterns of hypertrophy. The determination of regional wall motion abnormalities and other parameters of left ventricular function in patients with coronary artery disease with this technique could be a very important adjunct or even supercede such determinations now being accomplished by radionuclide angiography.

Proposed Course:

To overcome the above mentioned problem, a phased array transducer capable of use in the esophagus is being developed. This transducer will scan in a transverse plane allowing multiple parallel images to be obtained by moving the transducer up or down in the esophagus. The transducer must be small enough to be easily tolerated by patients and will need to interface to the Varian electronics.

Modifications to the existing reconstruction software will be made to permit use of the new images.

Groups of normal volunteers and patients with hypertrophic cardiomyopathy or coronary artery disease will be studied using this new method of echocardiography.

Publications and Abstracts:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00007-12 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Statistical Research in Clinical Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.K. Harris	Chief, Lab. of Applied Studies	LAS	DCRT
OTHERS:	G. Shakarji	Supv. Systems Analyst	DMB	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	L.M. Norton	Research Mathematician	LSM	DCRT
	G.Z. Williams	Institute for Health San Francisco, CA		
	S.S. Brown	Clinical Research Centre Harrow, England		
	R. Elin	Clinical Pathology	CC	
	T. Yasaka	PL Medical Service Dept Osaka, Japan		
	H E. Solberg	Rikshospitalet, Oslo, Norway		

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Applied Studies

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Univariate and multivariate time series models are being applied to various databases consisting of short series of measurements of serum biochemistries in healthy subjects. The purpose is to gain practical experience in the use of these statistical forecasting techniques for detecting real changes and trends within subjects, taking into account random biological variation and measurement error. The time scale of these series varies from weekly to 6-month and 12-month intervals between observations. Parallel computer-based simulation studies of these models are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigations into the asymptotic properties of a new stochastic model of linear change have begun, and this model is being applied to data from patients at the Clinical Center under long-term therapy.

PHS-6040
(Rev. 10-76)

Objectives:

To investigate applications of statistical theory, particularly the use of variance components, measures of within-person variation, and the theory of discrete time series, to the interpretation of clinical laboratory measurements and the evaluation of analytic procedures in clinical chemistry.

Recent Background:

During the past several years, the major effort in this project has been devoted to the application of recently developed mathematical-statistical models to three unique databases of serial biochemistries in healthy subjects. The smallest of these data collections, weekly measurements of 10 common constituents in 37 male volunteers over a 5-month period, arose from a cooperatively designed study with the Clinical Research Centre, Harrow, England. The two larger studies, in San Francisco and in Osaka, Japan, involve hundreds of men and women undergoing annual or semi-annual examination including clinical chemistry and hematology measurements. Running parallel with these studies has been a rapidly growing interest among many clinical laboratory workers and clinicians in the statistical bases of reference values commonly used in diagnosis and the evaluation of therapy. In particular, the need to take account of within-person biological variability over time is becoming more widely recognized among pathologists and others who interpret clinical laboratory reports.

Progress during FY 80:

A report on the behavior and usefulness of two univariate statistical forecasting models applied to short series of annual data from volunteers in the San Francisco health monitoring program has been published. A second report on analysis of weekly data from the Harrow, England study has also appeared in print during this past year. This paper concerned the development of statistical criteria for judging change between two successive measurements. In addition, two invited reviews have been completed and are awaiting publication, one on the statistical aspects of reference values in clinical pathology, the second on the uses and interpretation of regression, least squares and correlation in clinical laboratory research.

The application of multivariate and univariate random walk models to selected groups of measurements from the large-scale health monitoring program in Osaka, Japan is continuing. Preliminary findings indicate that the multivariate time series model is much more conservative in its interpretation of clinical laboratory results than is the univariate model. This agrees with recent computer-based simulation studies comparing univariate and multivariate reference regions applied to cross-sectional data. Similar simulation studies are now underway to compare time series models.

A new stochastic model of linear change, for use with short time series, has been programmed and will be applied to multiple biochemical series collected by the Arthritis and Rheumatism Branch, NIAMDD, in their studies of patients with systemic lupus undergoing long-term drug therapy. The unique feature of this model is its ability to estimate true changes in slope, free of effects of measurement errors and random "ups and downs". In cooperation with the Laboratory of Statistical and Mathematical Methodology, research has been undertaken into the asymptotic properties of this linear stochastic model, and the rapidity with which the model approaches asymptotic results under steady-state conditions.

Medical Significance:

The definition and estimation of analytical and biological variance components provides an essential basis for the objective interpretation of clinical laboratory tests in patients and healthy persons alike. The development, testing and routine use of univariate stochastic models to describe and forecast sequential results of laboratory tests in individual cases has proven useful when applied to periodic monitoring of healthy individuals as part of a general program of preventive medicine. Introduction of multivariate models for this purpose may prove even more valuable since many laboratory tests are interpreted as part of a multi-test organ battery or in concert with other, physiologically related measurements (e.g., calcium. total protein, albumin). However, the sensitivity and specificity of multivariate, as compared with univariate, methods -- whether for diagnostic or monitoring purposes -- needs careful assessment based on simulation studies and real patient data.

Future Course:

Current simulation studies on the statistical properties of univariate and multivariate time series models will continue and are expected to be completed during FY 81. A preliminary report on the application of multivariate random walk and homeostatic models to the data from the Japanese health-monitoring program is anticipated by the end of calendar 1980. The P.I. will also be engaged in several studies with collaborating scientists outside NIH concerning the transferability of reference values in clinical pathology. It is hoped that at least the methodology and preliminary results of such studies will be ready for presentation by the end of FY 81. The cooperative studies with the Arthritis and Rheumatism Branch on sequential forecasting of biochemistries in SLE patients will also be continued and initial reports are expected during FY 81.

Publications:

Harris, E.K. and Brown, S.S.: Temporal changes in the concentrations of serum constituents in healthy men. Annals of Clinical Biochemistry 16:169-176, 1979.

Harris, E.K., Cooil, B.K., Shakarji, G., and Williams, G.Z.: On the use of statistical models of within-person variation in long-term studies of healthy individuals. Clinical Chemistry, 26:383-391, 1980.

Harris, E.K.: Statistical aspects of reference values in clinical pathology. In Stefanini, M., M.D. (Ed.): Progress in Clinical Pathology, VIII. Grune & Stratton (in press). Grune & Stratton (in press).

Harris, E.K.: Regression, least squares and correlation. In Seligson, D., M.D. (Ed.): Handbook of Clinical Chemistry. CRC Press (in press).

Harris, E.K.: Further applications of time series analysis to short series of biochemical measurements. Proceedings of Workshop on Reference Values in Clinical Pathology. Helsinki, May, 1980 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00005-10 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Mathematical Models of Binding Equilibria

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS	DCRT
OTHERS:	R. Shrager	Mathematician, AMS	LAS	DCRT
	C. Erlichman	Clinical Associate, MD.	CP	NCI

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macrolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity and are studied to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Background:

Mathematical models of macromolecule-ligand binding equilibria have been investigated since 1966. This continuing effort has revised many of the concepts related to the binding of ligands to macromolecules particularly small ions to proteins. This project has produced an interactive methodology for the fitting of binding models to data and has developed other computer oriented tools for the analysis of data from laboratory experiments.

Significance to Biomedical Research:

The fitting of models to experimentally obtained data is a procedure used to estimate unknown parameters in mathematical models. The proper choice of a model, a choice of goodness of fit criteria, and the ability to estimate the unknown parameters is a basic need of biomedical research. The estimation of unknown biochemical parameters contributes to new biomedical insight and adds to basic scientific knowledge only if the fitted models represent the underlying biological process and the unknown parameters can be readily and accurately estimated. A thorough and continuing critique of such models and their appropriateness for the interpretation of current laboratory and clinical experiments is therefore essential to the growth of fundamental knowledge in these areas.

Progress in FY 80:

The cumulated findings of the previous AMS research in this area has been collected in the form of a summary report. This report details the various alternative models, graphical presentations of data, and algorithms for fitting models to data. Fitting algorithms are also available for fitting with other than the least squares criteria. The development of these criteria is detailed elsewhere. In FY 80 numerous requests for copies of exportable computer algorithms were honored and some consultation was provided. Some preliminary studies of cooperative binding in Aspartate Transcarbamylase are currently in the exploratory stage in collaboration with the Clinical Pharmacology Branch of NCI.

Proposed Course:

Applications of existing and new methodology to data analysis will continue to be made as they are requested by collaborating laboratories. Computer programs, reprints and reports will be provided to requesting consultees. Publication of the summary report is expected by late FY 80 or early FY 81. Analytical development of new models and continued research in this area (other than new applications) is not anticipated in FY 81.

Publications and Abstracts:

Fletcher, J.E., and Schubert, R.W.: On the computation of substrate levels in perfused tissues. Proceedings of the IVth Intl. Meet. of the Society of Oxygen Transport to Tissue. Budapest, Hungary, July 1980.

Fletcher, J.E.: Simulation and its use in biomedical applications. Distinguished Lecture Series (Videotape). Department of Biomedical Engineering, Louisiana Tech Univ., Ruston, LA, December 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00044-02 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Mathematical Modeling of Substrate Transport in Physiological Environments

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS	DCRT
OTHER:	M. Bieterman	Mathematician, AMS	LAS	DCRT

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested and satisfactory cost effective methods are used to explore the properties of these models. The results are interpreted in terms of microcirculatory physiology and are published in the scientific literature.

Objectives:

The objectives of this project are to develop mathematical models which can be used to simulate microcirculatory physiology and to explain, interpret and/or predict physiologic behavior and limits. Such models should lead to a better understanding of the biological control processes and should suggest improved clinical approaches to microcirculatory disorders.

Background:

The mathematical modeling of organ substrate supply by the microcirculation has been under study since FY 69. The substrate of primary interest is oxygen. Such modeling studies are aimed at the prediction of threshold and critical limits of substrate supply necessary to sustain cell function under a variety of physiologic conditions. The responses of models to varying blood flow, blood hemoglobin characteristics, tissue metabloic rate, tissue binding proteins, and other physiologic parameters have been examined. The complex interaction of microcirculatory geometry, nonlinear oxygen hemoglobin dissociation properties, intracellular binding proteins, and substrate dependent metabolic rates requires such a detailed description to achieve physiologic validity. These models require the numerical solution of a system of coupled distributed parameter models which are of a nonlinear type.

Significance to Biomedical Research:

Such modeling is necessary to predict the state of local tissue conditions since direct measurements are generally not possible and must be inferred from boundary observations. Studies of this type have the potential of predicting tissue oxygenation and reoxygenation in ischemia, hypoxia, anemia, coronary obstructions, sickle cell anemia, shock, and other conditions of substrate normal and abnormal physiology.

Progress in FY 80:

A parametric study of facilitated diffusion in an ideal tissue-capillary, steady-state arrangement was completed. A manuscript detailing the results has been published. Limitations in experimental knowledge of myoglobin function in muscle tissues have impeded further progress in model development. Extension of the current models to more complex time dependent systems seems inappropriate until further experimental knowledge is available to guide model extensions.

Proposed Course:

Mathematical techniques for the solution of the more complex models will continue to be explored in anticipation of forthcoming experimental data. The level of effort will be adjusted to section priorities and the rate of progress of experimental knowledge.

Publications and Abstracts:

Fletcher, J.E.: Facilitated diffusion in a Krogh cylinder model. Proceedings of the Annual ISOTT Meeting. La Jolla, California, July 1979.

Fletcher, J.E.: On facilitated oxygen diffusion in muscle tissues. Biophys. J. 29:437-458, March 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00035-04 LAS

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Mathematical Models and Simulation Programs in Physiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. Fletcher	Chief, Applied Mathematics Section	LAS DCRT
OTHER:	E. Harris	Statistician, Chief	LAS DCRT
	B. MacLees	Chief	MICU CC
	C. Tidball	Professor, Head Computer Assisted Medical Education	G. W. Univ.

COOPERATING UNITS (if any)

none

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.0	PROFESSIONAL: 0.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the identification and classification of various simulation programs used in physiology. These programs are being examined for utility in a clinical environment, for accuracy of representation of normal and abnormal physiologic conditions, and for the identification of areas of defective or missing physiologic relationships. The programs are being tested and evaluated. The outcome of the evaluation will be used to develop a more representative model to reflect the current state of knowledge in physiology.

Background and Objectives:

The objective of this project is to investigate the use of simulation programs in physiology as diagnostic and patient management aids to physicians and other clinical staff. Several biomedical researchers are using the programs to check their usefulness in physiology as diagnostic and patient management aids to physicians and clinical staff.

Significance to Biomedical Research:

Simulations offer the clinician the opportunity to try a proposed or alternative course of medical treatment on an ideal (computer) patient, without the attendant risk of injury to the actual patient.

Progress in FY 80:

This project was inactive in FY 80 due to the transfer of the previous principal investigator to another government agency. The physiologic simulators MACPUFF, MACPEE, MACMAN, and MACDOP are currently being maintained by LAS as active simulators for use by both the GWU Medical School computer assisted education projects and the USUHS medical training program. On-campus use of these simulators has been delayed due in part to a delay in staffing and full implementation of research directions in the MICU, CC, NIH.

Proposed Course:

The currently available physiologic simulators will continue to be maintained by LAS as active computer files. Experience will be be collected from current using groups as to the utility of such simulators in both a teaching and a clinical environment. If manpower and sufficient interest become available, efforts will be made to reactivate this project.

Publications and Abstracts:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00070-01 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Computation and Correlation of Substrate Levels in Perfused Organs with Experimental Measurements

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS DCRT
OTHER:	Roy W. Schubert	Assoc. Prof. Dept. of Biomedical Engineering	Louisiana Tech Univ.
	M. Jolly	Mathematician, AMS	LAS DCRT

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to study whole organ and tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Background and Objectives:

Each body organ has some ability to control or autoregulate its blood supply and thereby its substrate supply. The exact nature of these local control mechanisms are unknown. The objective of this project is to identify mathematical models of organ microcirculation having characteristics that correlate with experimentally obtained measurements. Such models can then be used to examine probable organ response to physiologic challenge.

Significance to Biomedical Research:

Direct measurement and observation of intact organ autoregulatory function are not possible. Mathematical models offer the only technique available for the study of possible autoregulatory mechanisms. The qualitative and quantitative nature of such mechanisms can be examined by means of appropriate models.

Progress in FY 80:

This project was begun in FY 80 as an extension of project Z01 CT00035 01 LAS. A previously published mathematical model which described perfused organ experiments was found to be mathematically incorrect. The initial step in this project was to obtain a mathematically correct solution of the existing mathematical model. This solution has now been obtained and is being explored parametrically. A preliminary report on its properties has been submitted to an international meeting.

Proposed Course:

It is anticipated that his project will have the following stages.

(a) A Reexamination of the Krogh cylinder model and its adequacy for the representation of perfused organ microcirculation.

(b) Develop exact mathematical solutions for the Krogh model that exhibit tissue axial diffusion and capillary axial diffusion for the steady state constant metabolic rate experiments with perfused organs.

(c) Develop or modify numerical algorithms that will compute substrate levels for nonconstant metabolic rates and other nonlinear effects.

(d) Develop algorithms for the direct comparison of distributed substrate level computations with experimentally obtained microelectrode measurements.

(e) Identify those critical ranges of parameters that control organ response to physiologic challenge.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00033-04 LAS

PERIOD COVERED

October 1, 1979 TO September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analysis of Coupled Transport and Biochemical Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. Bunow	Senior Staff Fellow	LAS DCRT
OTHERS:	J. Kernevez	Professor,	Univ. of Tech. Compiegne, France
	A. Kaplan	Research Biochemist	DCCP NCI
	D. Mikulecky	Professor,	Medical College of Virginia

COOPERATING UNITS (if any)

none

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates three fundamental problems in biology: (1) the role of dynamic patterns in embryology and evolution, (2) the kinetics of enzymes located in cell membranes, and (3) the kinetics of enzymes derived from hepatocyte cell lines which have been chemically transformed. The first area involves investigation of the role which simultaneous reaction and diffusion might play in the formation of some of the observed symmetries, polarities, and patterns in biological systems, such as organ shapes and surface markings. The second area involves investigation of enzyme kinetics with special emphasis on the role of cellular compartmentation on the interpretation of mechanisms. The third area involves the selection of instrumentation for data acquisition, display, and transmission, as well as mathematical analysis of kinetic studies on lactate dehydrogenase, an enzyme whose function and molecular form is altered in hepatocytes in tissue culture subject to chemical transformation. Digital computer simulation, numerical solution of partial differential equations and nonlinear regression analysis are the main tools in these investigations.

PHS-6040
(Rev. 10-76)

(1) Dynamic Patterns

Background and Objectives

Patterns polarizations and symmetries are often present in living organisms. These types of organization are absent in the ovum from which the organism develops How do they come about? The equations describing systems containing species which diffuse and undergo reaction possess solutions in which the development of organized patterns in the concentrations can be observed. Since reaction and diffusion are the predominant physico-chemical processes of living organisms, it is tempting to suppose that the two phenomena are linked. The objectives of this project are to develop numerical methods of solving reaction-diffusion equations in order to investigate the principles controlling pattern formation.

Significance to Biomedical Research

Patterns generated by reaction and diffusion have been hypothesized to play a role in a variety of developmental processes in biology The validity of these hypotheses have never been critically tested We address several critical questions about such patterns: (1) What is the relation between the form of the pattern and the shape of the domain? (2) What is the relation between the form of the pattern and the kinetics of the reaction? (3) Are the patterns unique?

Progress in FY 80

A numerical code using the finite element method developed in FY 79 has been applied to the computation of eigenfunctions of Laplacian operators on domains of irregular shape corresponding to certain biological structures. Analytical results were available suggesting that these eigenfunctions would resemble the patterns to be observed on these structures produced by reaction-diffusion processes. Comparison to actual reaction-diffusion patterns obtained numerically showed that the eigenfunctions do not provide an adequate approximation to the solutions of reaction-diffusion equations under most conditions. The patterns produced by the equations we have studied are nonunique. Whenever there are any stable patterns, there are at least two such patterns, and frequently many more. The task of selection among the diversity of such patterns is an added burden to any biological use of reaction-diffusion pattern-forming mechanisms. A manuscript summarizing application of reaction-diffusion models to pattern formation in Drosophila has appeared. A second manuscript describing numerical methods for enumerating the multiplicity of solutions was presented at an international meeting whose proceedings will be published. Two additional presentations have been solicited, and will result in additional publications of this material for a more mathematical audience.

Future Course:

The multiplicity of solutions observed during FY 80 requires further study. An algorithm has been adapted to trace out bifurcation diagrams for low dimensional dynamical systems. During FY 81 this algorithm will be generalized to be applicable to the finite element representation used for calculation of biological shapes.

(2) Kinetics of Enzymes

Background and Objectives:

Studies of the mechanism of membrane transport and bioenergetics have recently recognized the crucial role played by cell and organelle membranes. Nevertheless, no adequate treatment of the organization of reaction sequences in membranes is available. There remain great uncertainties both as regards the organization in the plane of the membrane as well as through its thickness. There are two objectives to this project. (1) to determine the extent to which the organization of a particular complex reaction sequence, that of active ion transport, can be inferred from external measurements of steady state and transient kinetics, and (2) to determine the role which organization in the plane of the membrane can play in regulating a second complex reaction sequence, that of oxidative phosphorylation in mitochodria.

Significance for Biomedical Research:

A great deal of effort is being expended in design, performance, and analysis of experiments in both of these research areas by many groups. Through the study of model systems, classes of measurements which are most likely to be informative will be indicated, as well as those whose outcome is unlikely to illuminate current controversies as to actual mechanisms in both of these areas.

Progress in FY 80:

The principal problem in treating complex systems is their very complexity. During FY 80 an adequate conceptual framework for the analysis of complex systems was acquired--network thermodynamics. The computational tool of dynamic network simulation was implemented, using the SPICE electrical network simulator, and effort begun to implement a still more powerful system--NET-2--which will permit a description of physiological and biophysical systems with material flows. Work in progress from FY 79 on the mechanism of ion transport has been completed, showing that external measurements do not suffice to infer the localization of the energization of an active transport mechanism. This result negates a large body of research which proceeds on the contrary assumption here shown to be incorrect. A manuscript describing this work is nearing completion. Network models of organization in the plane of the mitochondrial membrane show that it is unlikely that redistribution of sites of chemical reaction can significantly modulate the coupling of electron transport to ATP synthesis, negating an active hypothesis in this field.

Future Course:

During FY 81, NET-2 will become operational on the NIH computer. Collaborations with several laboratories on problems amenable to network description have begun. These include (1) metabolism and transport energetics in the renal medulla, (2) ionic osmoregulation in in erythrocytes, and (3) excitation-contraction coupling in cardiac muscle.

(3) Kinetics of Lactate Dehydrogenase(LDH) from Chemically Transformed Hepatocytes

Background and Objectives:

When the enzyme LDH is isolated from control and chemically transformed hepatocytes grown in tissue culture, there are differences both in amount of activity and modulation thereof by an inhibiting product. The objective of this project is to characterize the differences in LDH from various sources, emphasizing particularly the differences between normal and transformed cells.

Significance to Biomedical Research:

A hematological test for the presence of cancer cells would be of obvious value. One approach to the design of such a test is to seek readily identifiable differences between cellular products of normal and tumor cells.

Progress in FY 80:

During FY 80 a phenomenological model was developed to permit quantitative differentiation between LDH from different sources. This model, applied to kinetic data on early and later inhibition of LDH by a reaction product, yielded consistant and reproducible results. An abstract has been presented and a manuscript describing this work is near completion.

Future Course:

During FY 81 the experimental study of the enzyme will be more highly automated by the incorporation of a microcomputer which can both capture data from the stopped-flow spectrophotometer as well as transfer that data to the NIH Computer Systems for further analysis. Software and hardware specifications for this computer will be completed, and the procedures for operation using it will be developed. With the new apparatus, the experimental study can be easily extended to enzyme from new cell types.

Publications:

Bunow, M.R., and Bunow, B.: Phase behavior of ganglioside-lecithin mixtures: Relation to dispersion of gangliosides in membranes. Biophys. J. 26:325-337, 1979.

Bunow, B.: Cellular enzymology: Effect of Compartmentation on steady state enzyme kinetics. J. Theor. Biol., (in press).

Bunow, B., Kernevez, J.P., Duban, M.C., Joly, G., and Thomas, D.: Pattern formation by reaction-diffusion instabilities: Application to morphogenesis in drosophila. J. Theor. Biol., 1980 (in press).

Bunow, B., and Kernevez, J.P.: Numerical exploration of bifurcating branches of reaction-diffusion equations. Workshop on Chemical Instabilities, Univ. Texas, Austin, 1980 (in press).

Abstracts:

Kaplan, A., Weiss, E., and Bunow, B.: Multiple molecular forms of lactate dehydrogenase: Demonstration by kinetic analysis and iso-electric focusing. Fed. Proc. 39 (6) #3208, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00004-09 LAS

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.W. Pottala	Elec. Engineer	LAS	DCRT
OTHERS:	J.J. Bailey	Chief, MAS	LAS	DCRT
	I. Yaar	Visiting Scientist	MNB	NINCDS
	W.C. Van Arsdale	Pharmacologist	DDB	FDA
	J. Wolpert	Eng. Aid	LAS	DCRT

COOPERATING UNITS (if any)

Medical Neurology Branch, NINCDS
Division Cardio-Renal Drug Products, FDA

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Medical Applications Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1.0	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, and electromyogram.

Background and Objectives:

Since FY 72 the LAS Laboratory minicomputer system (MAC 16) has been developed and utilized for various projects including (1) the construction of physiologic simulation models and (2) the processing of physiologic signals. Since FY 72 the system has been interfaced with the Marquette tape drive (for routine ECG's from the Clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch-filter network; with a real time spectral analyzer and ensemble averager; and with a neural control panel for simulation of neural networks (FY 75) and central nervous system subsystems (cerebellum, FY 76).

A general advantage of this system is that an investigator can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained. This was demonstrated in electromyograms from subjects on a muscle fatigue protocol studied by the National Institute of Occupational Safety and Health (FY 75). This facility was also used for electrocardiogram (ECG) and ventricular pressure data in monkeys (FY 76) and also ECG data from Glasgow Royal Infirmary (see ECG section).

Progress During FY 80:

An operating system for the MAC-16 system has been developed which provides the user with easy access to compilers and major programs, handles I/O for all peripheral devices, and automatically allocates system facilities and storage during execution of user programs.

The hardware simulation effort has continued to make available to the physiologic researcher cost effective ways to investigate and help teach basic cellular behavior.

The Medical Neurology Branch, NINCDS is studying the use of electromyograms to determine muscle fiber conduction velocities and to investigate disease states. Preliminary analog to digital conversion and spectrum analysis has been performed on the data, to define the filtering and amplification requirements of the data collection (Reference 1).

The Division of Cardio-Renal Drug Products, FDA is investigating the early detection of cardiac toxicity resulting from drug therapy. Electrocardiograms are being used to determine the sensitivity of detection. Programs have been written and preliminary analog to digital conversion of the data has been done to provide data for the analysis programs.

Currently the effect on cardiac behavior of various drugs, in particular, cancer chemotherapy agents, is monitored by a single lead electrocardiogram (ECG) in animals. The end point for cardiac toxicity is terminal ventricular tachycardia. The current study is investigating multiple lead ECG's and the computer analysis of this data to provide more sensitive and accurate end-points for drug effects.

Significance:

In some simulation models, certain pieces or functions can be split off and implemented in hardware circuitry or in a set of microprocessors. This has several advantages. First, parallel processing is allowed, which can shorten computing time and make interactive model testing feasible. Second, the hardware circuitry or microprocessors are usually quite inexpensive. And third, some models are so complicated and extensive that their implementation on a large scale digital computer is not feasible; whereas with hybrid computing, such models may be achieved. An example was the model of the Purkinje network in the alligator cerebellum which required a system of 35 cells connected by nonlinear differential equations (completed in FY 76). Another example was the simulation of retinal cone cells (described FY 79).

Proposed Course:

The MAC-16 system will have continued use for ECG processing from the Framingham Heart Study (see project report on electrocardiography).

Further investigation of the FDA protocols on cardiotoxicity will proceed when an engineering aid returns in FY 81.

Hardware modeling efforts are to be temporarily suspended until a suitable project and co-investigator is found.

The EMG study is to be continued with emphasis on characterizing disease states.

Publications and Abstracts:

Yaar, I., Shapiro, M., Mitz, A.R., and Pottala, E.W.: (abstract) Introducing a new computer assisted technique, for measuring muscle fiber conduction velocities at full interference pattern. American Neurological Association, Sept. 1980.

Vallerga, S., Covacci, R., and Pottala, E.W.: Artificial cone responses: A computer-driven hardware model. Vision Research, 20: 453-457, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00042-02 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.W. Pottala	Elec. Engineer	LAS	DCRT
	J.L. Costa	Medical Officer	CN	NIMH
	C.E. Fiori	Physical Scientist	BEIB	DDR
	M.A. Douglas	Computer Systems Analyst	LAS	DCRT
OTHERS:	K.E. Gorlen	Elec. Eng.	CSL	DCRT
	R.D. Leapman	Physicist	BEIB	DDR
	C.R. Creveling	Chief	LC	NIAMDD
	E. Silbergeld	Chief, Neurotox. Sect.	LP	NINCDS
	C. Gibson	Elec. Eng.	BEIB	DDR

COOPERATING UNITS (if any)
Biomedical Engineering and Instrumentation Branch, DRR, Computer Systems Laboratory, DCRT, Clinical Neuropharmacology Branch, NIMH Laboratory of Chemistry, NIAMDD, Laboratory of Experimental Atherosclerosis, NHLBI, Section on Neurotoxicology, NINCDS

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	2.0	.1

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves collaboration of LAS with BEIB and several NIH Institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally X-rays and electron energy loss spectra, derived from biological specimens studied in an analytical electron microscope.

Background and Objectives:

BEIB has purchased a 200 kilovolt scanning transmission electron microscope which can produce both pointwise spectral data (electron energy loss, X-ray) and matrix images containing spectral information. It will be connected to a KEVEX 7000 spectrometer and with various other hardware interfacing to a DEC 11-60 computer system. The basic hardware configuration and systems software are being developed by CSL.

An array processor (CSPI MAP200) acquired by LAS is also being incorporated into the system. The speed of the array processor should make several procedures fast enough to become part of normal analyses. For example, a complex FFT (1024) can be accomplished in only 20 milliseconds; a Gaussian curve fitting can be shortened from 8 hours to 10 minutes. Hence LAS anticipates that many image processing algorithms which can be developed off-line on the DEC-10 and for DeAnza systems can subsequently be implemented on the array processor and allowed to operate almost in real-time.

BEIB has planned this research facility in collaboration with NIMH, NHLBI, NIAMDD, NINCDS, and DCRT to develop pioneering applications of analytical electron microscopy. This can be accomplished because:

1. The high energy beam (200Kev) will provide a significant increase in the signal-to-noise ratios of the chemical information and should make possible the analysis of hydrated specimens.

2. The assemblage of hardware and computer systems allows rapid data acquisition and the complex processing necessary to extract chemical information from the raw data -- both heretofore unavailable at other installations.

Of particular interest are the electron-energy loss spectra (inelastically scattered electrons) which contain information about the chemical composition of the specimen, the back-scattered electrons, and the elastically scattered electrons (both related to the mass density of various specimen regions). The physics of these various types of electrons as well as the measured specimen current and secondary electrons emitted needs to be elucidated in order to formulate the proper mathematical or statistical models which can combine this information into a "true" or corrected elemental map on a pixel-by-pixel basis. These models should adjust for contributions of neighboring pixels as well as a Poisson process in some cases. The relationship between elemental (energy-loss) peaks, zero-loss (transmission) peaks, and the plasmon peaks as well as the background contribution requires further exploration and quantification.

The potential resolution for chemical analyses of the system is in the range of 10^{-6} to 10^{20} gms. and the spatial resolution is in the order of 100 - 1000 square Angstroms. In addition the system can construct maps of 1024 x 1024 pixels. The further development of this tool will require a new kind of image processing which will differ radically from the usual sort applied to nuclear medicine, X-ray devices, and ultrasound.

Progress During FY 80:

The array processor has undergone extensive testing and a fault has been detected in many of the printed circuit boards and also the power supply. The entire unit was shipped back to the factory; the vendor (CSPI) has extended the warranty indefinitely until the faults have been corrected.

The DeAnza image processing system has been installed and software written. (See project report on Nuclear Medicine).

The edge detection option of the PICTUR package has been used to locate dense bodies in digitally acquired electron micrographs of platelets, and to compute their mass thickness.

A program, ALIGN, has been written to spatially align pairs of digitized images. This program has been used to produce composite elemental maps from paired pre-edge and fluorine K-edge energy filtered images (Reference 1).

Lung macrophage images have been displayed on the system and, through use of selective intensity table manipulation, fine structure has been visually enhanced.

Significance:

The ultimate biological goal is to relate structure and function at the ultramicroscopic, molecular, and chemical levels. Certain active molecules (e.g., enzymes, neurotransmitters, hormones, antibodies, etc.) -- can be tagged with appropriate labels (e.g., fluorine) -- and then localized and quantified within cells by means of this tool. It should be possible as well to determine the distribution of double bonds within membranes, microtubules, and cytoplasmic organelles. The distribution of elements of great biological importance (viz, calcium, magnesium, nitrogen, sulfur, and oxygen) also can be determined.

Thus, the research potential of this tool has widespread applications in all areas of biology concerned with ultrastructure, much as the development of the imaging capability of the electron microscope itself has provided important insights in almost every area of biology.

Proposed Course:

The study of the basic physics and the formulation of appropriate mathematical/statistical models needed to achieve the analytical capabilities will require extensive work with phantoms, i.e., specimens prepared by such means as vacuum evaporation, which are very thin and of known composition. There will need to be extensive studies of the signal/noise ratio in phantoms and in biological specimens. Potential problems with contamination and with specimen destruction by the high energy beam also need to be studied. Sophisticated algorithms for element recognition and location, image enhancement, etc., need to be designed and, where practicable, implemented on the array processor for rapid turnaround.

LAS proposes to undertake, in collaboration with BEIB and the other participating Institutes, some of these objectives after the combined system is operational. In particular, development of image processing algorithms, heretofore dependent upon data from other installations (Bell Labs, Brookhaven, etc.) can be accelerated (Reference 1).

Publications and Abstracts:

Douglas, M.A., Hui, S.W., Costa, J.L., and Bailey, J.J.: Computerized processing and subtraction of energy-filtered electron images as an aid to elemental analysis. Proceedings of the IFSEM Pacific Regional EMSA/MAS Meeting 1980 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00010-04 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Nonlinear Equations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. I. Shrager	Mathematician	LAS	DCRT
OTHERS:	G. D. Knott	Computer Specialist	LSM	DCRT
	J. E. Fletcher	Research Mathematician	LAS	DCRT
	R. W. Hendler	Biochemist	LCB	NHLBI
	A. Schechter	Biochemist	LCB	NIAMDD

COOPERATING UNITS (if any)
LB, NHLBI
LSM, DCRT

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are developed for solving nonlinear equations frequently encountered at the NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis, and the efficient treatment of sparse systems, are also considered.

PHS-6040
(Rev. 10-76)

Background and Objectives:

The objective of the project is to develop methods for solving the nonlinear equations frequently encountered in descriptions of biomedical problems at the NIH. General categories of problems for which solutions were developed here (in part or wholly) are nonlinear least squares with linear constraints, nonstiff and stiff ordinary differential equations, and nonlinear curve fitting in norms other than least squares. In addition, every project with which this one interfaces (i.e., collaborations) presents its own set of special equations which must be solved, in either the analytic or numerical sense. Methods which prove to be of general utility are developed into accessible computer programs or routines, e.g., MODELAIDE and MLAB.

Significance to Biomedical Research:

These methods are essential for the resolution of problems of of data analysis in metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Progress in FY 80:

(1) Projects initiated within the DCRT

A version of MLAB using norms other than least squares is under development in collaboration with G. Knott, of LSM. This method is an extension of the current MLAB least squares routine, requiring a minimum of added code.

The MLAB differential equation solver is being revised to conform to practices recommended by L. F. Shampine (Implementation of implicit formulas for the solution of ODE's, SIAM J. Sci. Stat. Comput., Vol. 1, N. 1, March 1980, pp. 103-118). As an outgrowth of these revisions, a new step size selection algorithm is under development.

A method of analyzing a set of spectra by singular value decomposition is under development based upon data being provided by Richard Hendler (NHLBI), Joseph Rifkind (NIA, Baltimore) and Alan Schechter (NIAMDD). The object is to detect the number of titrating species in a mixture, and some information about each, e.g.: What is its midpoint potential or pK value? What is the appropriate titration formula (Henderson-Hasselbach, Nernst, Adair)? What is the spectrum of each species? The problem is complicated by noise, instrument distortions, and material impurities.

(2) Collaborative projects outside DCRT FY 80

1. Analysis of Experimental Spectra, R.W. Hendler, O.Y. Setty, LB, NHLBI. This project is concerned with the detection of anomalous acid production when membranes were oxidized. The unknown substances that give rise to the acidification are of interest. The principal error source in Dr. Setty's experiments on oxygen uptake by reconstituted membranes seems to be the noise and instrument distortion in the measurement of small but rapid changes in pH. Computer analysis has served to point out the problem areas, but the solution is now an engineering problem. A manuscript describing this work has appeared and further work on Singular Value Decomposition (SVD) of a set of spectra is now in first draft manuscript stage.

2. Hemoglobin saturation analyzer, R. Berger, TD, NHLBI (with additional colleagues from Italy and DRS engineers)
The idea of using infra-red lasers or LED's to analyze whole blood is controversial. There may or may not be too much scattering to extract a usable signal. DRS is building a prototype to test its feasibility.

3. Sickle cell hemoglobin, Alan Schechter, Connie Noguchi, LCB, NIAMDD
Red blood cells of homozygous sickle-cell anemia patients assume a sickle shape because of the gelation of sickle hemoglobin in the deoxygenated state. Theory indicates that this should also be observed in the heterozygous case, but it isn't. It is hoped that spectral analysis of the various experimental conditions will reveal states of hemoglobin gelation that have previously gone unnoticed.

4. Cell Sorter, John Wunderlich, Steve Dower, I, NCI
A mechanism for fluorescent tagging of cells predicts that the the tagged cell intensity distribution is a convolution of the untagged (blank) distribution and the distribution of tag.
J. Wunderlich and S. Dower have performed an experiment where convolution might actually be verified using cells with signals that are virtually independent of each other, one to be regarded as the blank, the other as the desired response.

5. Phytic Acid Titration, William Evans, Dept. of Agriculture, New Orleans
On the basis of data from Evans' lab, a model of H+ binding to phytic acid was constructed that explains his data and predicts the concentration of various liganded states. Phytic acid is a chelating agent which may be a factor in metal-deficiency diseases, especially in countries where seeds form a large part of the diet. Dr. Evans is now writing a first draft manuscript, merging the experimental and computer results.

Proposed Course:

In FY 81 an MLAB general-norm curve-fitter will be tested, along with the refined differential equation solver. Computer methods for the SVD analysis of spectra should be ready for application to the cytochrome and sickle-cell projects. At least two papers will be forthcoming on acid production by oxidized membranes, one characterizing the spectrum and describing the effects of oxidation, the other presenting analysis of the substance in question by various spectral techniques. The hemoglobin saturation analyzer will be built and tested. The first analyses of spectra in the sickle-cell study will begin in FY 81. After the convolution process is convincingly demonstrated in the analysis of cell sorter data, a search will begin for the best method to numerically deconvolute the appropriate signals. The phytic acid titration study will be followed by attempts to assess its effects on various trace metals in the human diet.

Publications and Abstracts

1. Hendler, R.W. and Shrager, R.I.: Potentiometric analysis of escherichia coli cytochromes in the optical absorbance range of 500 nm to 700 nm. J. Biol. Chem. 254, 22:11288-11299, November 25, 1979.

2. Shrager, R.I. and Hill, E.: Non-linear curve-fitting in the L-1 and L-infinity norms. Mathematics of Computation 34, 150:529-541, April 1980.

Berk, P.D., Baschke, T., Shrager, R.I., and Waggoner, G.G.: Effect of phenobarbitol on the early labeling of plasma bilirubin in Gilbert's syndrome. Clin. Res. 28, 2, April 1980.

Setty, O.H., Hendler, R.W., and Shrager, R.I.: Respiration-driven proton ejection by reconstituted E. coli succinoxidase vesicles. Fed. Proc. 39, 6, p. 1706, May 1, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00045-02 LAS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Numerical Approximation Techniques for the Solution of Reaction - Diffusion Systems in Biology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Bieterman	Mathematician, AMS	LAS DCRT
OTHER:	J.E. Fletcher	Chief, AMS	LAS DCRT
	B. Bunow	Biomathematician, AMS	LAS DCRT
	I. Babuska	Professor, Institute of Physical Science and Technology	Univ. of Md.

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The fundamental tools needed to compute the solution of model reaction-diffusion systems are the mathematical techniques and related software used to solve nonlinearly coupled partial differential equations via computer. This project provides two interrelated forms of mathematical support for ongoing laboratory modeling of biological processes: (1) new, theoretically sound and computationally efficient numerical solution techniques are investigated and developed into computer programs, and (2) existing methods and computer programs are modified and implemented to solve specific models.

Background:

The mathematical models describing reaction, diffusion, and transport processes in biological and physicochemical systems consist of systems of nonlinearly coupled ordinary and partial differential equations. Specific mathematical techniques and numerical methods needed to treat many of those equations either do not exist in the present literature, or require a very large amount of computer time, making their implementation economically impractical. The development of new techniques, and continuing attempts to improve the efficiency of known algorithms are the objectives of this research area.

Significance to Biomedical Research:

The types of equations being studied are used to model substrate transport in the microcirculation and embryologic pattern formation. Other biomedical application areas include population dynamics of ecological systems, population genetics, nerve impulse transmission, and tumor growth, vascularization, and necrosis. The effective modeling of physiologic processes requires efficient methods for the numerical solution of systems of lumped or distributed parameter models. Such models are required to describe the complex interacting systems with flow, diffusion, and chemical reaction which are basic to normal and pathophysiology. Collection and characterization of solution techniques also makes them available to the NIH biomedical community as research tools.

Progress in FY 80

Investigation of numerical methods used to solve coupled systems of linear and nonlinear partial differential equations has continued. Our collection of computer programs being tested includes implementations of both finite difference techniques and finite element methods.

Further testing of the finite element codes implemented on the NIH IBM 370 System was completed. These programs are useful and productive tools in biological modeling in that a variety of problems on irregular-shaped, two-dimensional regions can be solved. It was found in parametric studies of eigenvalue problems associated with biological pattern formation that visual inspection of graphically displayed output often leads to false conclusions about the accuracy of a computed approximation. Objective criteria for approximation error are being developed.

Research of the "method of lines" approach for the solution of time dependent reaction-diffusion systems has continued. The procedure involves finite element discretization in the spatial variables and a novel, implicit, Runge-Kutta type discretization in the time variable. Space and time errors are estimated and controlled adaptively by the computer during the solution process.

The mathematical theory required for the adaptive solution of single, steady state problems has been extended to include coupled systems of linear, time dependent equations. Preliminary versions of programs implementing these concepts for the linear response of systems in a one dimensional, uniform medium have been written. Theoretical and computational attention will now be focused on the extension of these results to linear and nonlinear systems in nonuniform media.

Proposed Course:

Mathematical support of ongoing modeling projects will continue in the forms of research of adaptive finite element and finite difference schemes and further development and application of known techniques to specific models. These efforts will continue at levels determined by section priorities and manpower.

Publications and Abstracts:

None

Projects and Activities
FY 1980
Physical Sciences Laboratory

George H. Weiss, Chief

CLINICAL RESEARCH AND EPIDEMIOLOGY

Consulting Services. George H. Weiss (PSL); N. Gershon (PSL); J. Shapiro (CC); A. Pikus (CC); W. F. Caveness (Walter Reed); K. Kohn (NCI); L. Muenz (NCI); R. A. Brooks (NINCDS). This project involves several different collaborative consultations. We have continued to analyze data on 1221 head injured Vietnam veterans, in particular the occurrence and time dependent patterns of post-traumatic fits in groups of veterans having recognizable categories of injury. A collaborative audiometry study has begun with members of the Clinical Center. The first such study is a comparison of parameters between patients with osteogenesis imperfecta, family menbers of such patients, and normals. Together with Dr. L. Muenz, PSL scientists have developed a systematic technique for deriving the joint distribution of order statistics and moments of the underlying distribution, using generalized functions. A study on angular interpolation in computerized tomography was completed, in which the method of phantom views was found to be the best of several competing possibilities. A difficult combinatorial problem arising in the analysis of the fractionation of DNA strands was solved and will be applied to experimental data now being collected.

LABORATORY INVESTIGATIONS

Theory of Biochemical Separation Techniques. George H. Weiss (PSL). This project applies mathematical methods to the interpretation of data from, and the design of, biochemical separation methods. The only result obtained this past year was a negative one--the impossibility of measuring rate constants by affinity chromatography without auxiliary experiments. This is contrary to an analysis in the literature which could not be substantiated experimentally by an NIH biochemist.

Actin in Nonmuscle Cells/Biophysical and Biochemical Studies. Stephen L. Brenner (PSL); E. D. Korn (NHLBI). This is an experimental investigation of the protein actin which is believed to be important in determining the shape of red blood cells. Current experiments have elucidated the nature of the spectrin/actin complex.

Theory and Application of Nuclear Magnetic Resonance Spectroscopy. James A. Ferretti (PSL); G. H. Weiss (PSL); E. D. Becker (DRR); R. J. Highet (NHLBI); G. R. Marshal (Washington University); J. L. Costa (NIMH). Studies are conducted on the structure and function of biologically interesting molecules. A considerable amount of time was spent on setting up a new 360 MHz NMR spectrometer which will allow much higher resolution by means of two-dimensional Fourier spectroscopy. Investigation of the configuration and mode of action of bleomycin are continuing. Further analyses of correlation spectroscopy were made, and research into optimal design of experiments to measure spin-lattice relaxation times is continuing.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal (PSL). Laser methods are developed for measuring physical and biological properties. Two general areas are under investigation. The first is the use of laser Doppler techniques to measure blood flow in capillaries, and the second is the use of laser light scattering to measure elastic properties of gels. A theory has been developed to relate scattered light measurements to underlying flow properties. The theory has been checked and found to be in good agreement with experiments on artificial systems.

Cell Motility and Chemotaxis. Ralph J. Nossal (PSL); L. Lipkin (NCI). This project studies the theoretical basis of macroscopic assays of leukocyte chemotaxis, and develops computer assisted tracking techniques with which to collect data. Collaborative experiments are presently being carried out to estimate microscopic statistical parameters of leukocytes.

Theory and Measurement of Intermolecular Forces. V. Adrian Parsegian (PSL); A. N. Schechter (NIAMDD); M. Prouty (PSL); R. P. Rand, L. Lis, N. Fuller (Brock University). This project consists of a closely linked theoretical and experimental investigation of forces in phospholipid bilayer membranes. Experiments on a variety of phospholipids and phospholipid/cholesterol mixtures have led to the conclusion that the dominant force between membranes that are stable in water is due to the work of removing water between the surfaces. Similar techniques to those used in the measurement of membrane forces can be used to determine protein interactions. Presently investigations are being carried out on the energetics of deoxygenated sickle cell hemoglobin using techniques developed in this project.

Studies in Mathematics and Statistics. George H. Weiss (PSL); J. E. Kiefer (PSL). This project involves a miscellany of investigations. Considerable time was spent in studying properties of random walks useful for the description of polymer configurations.

Interaction of Cell Surface Proteins with the Cytoskeleton. Nahum Gershon (PSL); B. Bowers (NHLBI). In this project electron microscopic images are used to detect cytoskeletal proteins under cell membranes. Work on this project has just begun and programs are presently being written for the analysis.

Analysis of the Effects of Cytochalasin B and D on the Distribution of Groups of Insulin Receptor Sites on Rat Adipocytes. Nahum Gershon (PSL); L. Jarett (University of Pennsylvania). In this project the distribution of insulin binding sites on the surface of rat adipocytes is studied. The receptor positions were digitized from electronmicrographs and found to be clustered.

Quantitative Analysis of the Electronmicroscopy of Cells and their Plasma Membranes. Nahum Gershon (PSL); R. J. Nossal (PSL); K. Porter (University of Colorado). Quantitative methods are developed for digitizing the positions of proteins on membranes, or of other labelled particles obtained from autoradiographs. These will be applied to analyze the localization of IgE receptors on cell membranes.

Diffusion of Molecules on Cell Surfaces. Nahum Gershon (PSL); B. Aizenbud, (Beer Sheva University). This is a theoretical study of the role of cell curvature on diffusion. A model surface was constructed to mimic the geometry of microvillous membranes. Results of this study indicate that the assumption of planarity of the surface does not lead to large differences in the calculation of diffusion constants.

COMPUTER RESEARCH AND TECHNIQUE DEVELOPMENT

Computerized Typesetting of Scientific Papers. V. Adrian Parsegian (PSL); Nancy Crawford (PSL); P. Miller (OD); M. Douglas (LAS); M. Horton (LAS). In this project a link has been established between commonly available word processors and typesetting computers. This allows authors to typeset their own articles and can lead to greatly reduced printing costs as well as greater accuracy. A book has been set in this way and feasibility has been demonstrated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Consulting Services

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: George H. Weiss, Chief, PSL
Other: N. Gershon, Ph.D., PSL
J. E. Kiefer, PSL

COOPERATING UNITS (if any) R. A. Brooks, Ph.D., SN, NINCDS; Larry R. Muenz, Ph.D., BR, NCI; J. Shapiro, M.D., CC, DIR; A. Pikus, M.Sc. CC, OPD; W. F. Caveness, M. D., Walter Reed; K. Kohn, Ph.D., LMPH, NCI; A. Talbert, OBE, NINCDS; Y. Hirshaut, M.D., Sloan-Kettering Institute

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology

TOTAL MANYEARS: 1.0	PROFESSIONAL: 0.9	OTHER: 0.1

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Members of the PSL provide consulting services in different areas of applied mathematics and the physical sciences to researchers at NIH and elsewhere. We have continued research on different interpolation methods in computerized tomography, in particular developing the theory of phantom views which has been found to diminish some artifacts in image reconstruction. Another research area has been the demonstration that generalized functions can be used to simplify calculations of joint distributions of order statistics and moments for arbitrary probability distributions. We have completed work and furnished a solution to combinatorial problems of considerable difficulty that arise in pharmacology. A joint project was started with members of the clinical center on the quantitation of audiometric methods, with specific application to diagnosis of osteogenesis imperfecta. Further epidemiological investigations were made on a data base of 1221 head-injured Vietnam veterans, with particular emphasis on post-traumatic epilepsy.

PHS-6040
(Rev. 10-76)

Consulting Services

In a continuing study of image reconstruction in computerized tomography, we have developed theory for errors due to the necessity of interpolating angular information. We have also considered the possibility of diminishing these errors by using the technique of interpolating phantom views between views obtained from real data, and found that certain artifacts can be decreased in this way. An empirical study has established the optimum number of phantom views in the trade off between computing time and accuracy.

Together with Dr. Larry Muenz we have developed a method of calculating joint distributions of a large class of statistical parameters, using generalized functions.

A complete solution has been furnished to Dr. Kurt Kohn of a combinatorial problem arising from the design of experiments relating to the fractionation of DNA strands by alkaline elution. The mathematical technique used in the solution is unique and will have much wider applications. The experiments are being performed presently and the mathematical and experimental results will be written jointly.

We have started a joint project with Dr. Jay Shapiro and Anita Pikus of the Clinical Center of the use of audiometry in the diagnosis of diseases such as osteogenesis imperfecta. A considerable amount of time was spent on trying to quantitate data collected on the instrument presently used in the Clinical Center. We could not reliably perform the A/D conversion using a digitizer so the project has temporarily stopped until an A/D converter is fitted directly to the audiometer.

A collaboration with Dr. William Caveness has continued on the examination of data on head-injured veterans of Vietnam. We completed a study on the relation between injury parameters and subsequent language and motor deficits. Our present interest is in developing the relation between severity of injury and the occurrence and time history of post-traumatic epilepsy. Planning is presently underway for the examination of as many of this groups of veterans as can be found to determine the more permanent effects of injury. In connection with this phase of the project we have developed a technique for estimating the amount of permanent brain damage with information furnished by CAT scans.

Together with Dr. Y. Hirshaut we have examined ways to combine immunological tests that differentiate between different leukemias, so as to increase their accuracy. The available data showed that this was possible but more data is needed to elucidate correlations that might have been missed.

Keyword Descriptors: Image reconstruction, computerized tomography, interpolation, fractionation, generalized functions, audiometry, head injuries, post-traumatic epilepsy.

Publications:

Bunow, B., Line, B. R., Morton, M. R., Weiss, G. H: Regional ventilatory-clearance by xenon-scintigraphy: A critical evaluation of two estimation procedures. Journal of Nuclear Medicine 20:703-710, 1979.

Gail, M. H., Weiss, G. H., Mantel, M., O'Brien, S. J.: A solution to the generalized birthday problem with application to allozyme screening for cell culture contamination. Journal of Applied Probability 16:242-251, 1979.

Brooks, R. A., Talbert, A. J., Weiss, G. H.: The offset detector in computed tomography: Interleaving vs. separate processing. Computer Aided Tomography and Ultrasonics in Medicine. North-Holland, Amsterdam, 1979, 7-9.

Rish, B. L., Dillon, J. D., Meirowsky, A. M., Caveness, W. F., Mohr, J. P., Kistler, J. P. Weiss, G. H.: Cranioplasty: A review of 1030 cases of penetrating head injuries. Neurology 4:381-385, 1979.

Meirowsky, A. M., Caveness, W. F., Rish, B. L., Dillon, J. D., Mohr, J. P., Kistler, J. P., Weiss, G. H.: Definitive care of cerebral missile injuries crossing the midline. Military Medicine 145:246-250, 1980.

Mohr, J. P., Weiss, G. H., Caveness, W. F., Dillon, J. D., Kistler, J. P., Meirowsky, A. M., Rish, B. L.: Language and motor deficits following penetrating head injury in Vietnam. Neurology (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00014-13 PSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Theory of Biochemical Separation Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: George H. Weiss, Chief, PSL

COOPERATING UNITS (if any)

M. S. Lewis, Ph.D., BEIB

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology

TOTAL MANYEARS: 0.1	PROFESSIONAL: 0.1	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project explores the use of mathematical techniques and models to interpret data from biochemical separation experiments. Very little work was done on this project during the past year. Preparations were made to run experiments to determine moments of the distribution of molecular weights in proteins as measured by equilibrium sedimentation. A study of the feasibility of measuring rate constants by affinity chromatography was concluded with a generally negative finding unless auxiliary information is available.

Keyword Descriptors: Biochemical separation techniques, equilibrium sedimentation.

Publications:

G. H. Weiss: Can one measure rate constants using chromatographic methods? Separation Science (to appear).

Actin in Nonmuscle Cells-- Biophysical and Biochemical Studies

Actin is one of the major proteins of the cytoskeleton of all eukaryotic cells. As such, it is involved in many different motile processes and in the regulation of cell shape and cell organization. Actin is a globular molecule of molecular weight 42,000 that polymerizes into double helical filaments under ionic conditions similar to those of the cytoplasm of cells. It is in this polymerized form (microfilaments) that actin presumably functions in non-muscle cells just as it is the polymerized form of actin (thin filaments) that function in muscle contraction. However, in contrast to the situation in muscle, most of the actin in non-muscle cells is non-polymerized and its polymerization is both temporally and spatially regulated so that the microfilaments occur in the cell when and where they are needed for specific motile events. One proposed mechanism for the regulation of actin polymerization is the interaction of non-polymerized actin with complexes that facilitate the polymerization of actin. An intriguing model for such a nucleating complex is the complex of spectrin and actin that can be isolated from red blood cells. This year, we have used a number of specific problems to determine the mechanism by which the spectrin/actin complex facilitates the polymerization of actin and to examine some of the fundmental events of actin polymerization that naturally occurring modulators might affect.

(1) Nucleation of actin polymerization by spectrin/actin complex: Reports from other laboratories had suggested that erythrocyte spectrin could induce the polymerization of actin under conditions in which actin would not polymerize alone. Last year we showed that this putative property of spectrin was, in fact, attributable not to spectrin but to a complex of spectrin and actin. This year we have shown that the effect of the complex is to nucleate actin polymerization, i.e. to accelerate the polymerization of actin, and to lower the concentration of actin necessary for polymerization to occur (lower the critical concentration). The spectrin/actin complex, therefore, may be a prototype for natural nucleating centers in cells. The spectrin/actin complex accounts for all of one class of high affinity cytochalasin-binding sites in the erythrocyte. From a combination of these data, knowledge of the actin content in the erythrocyte and evidence discussed below that cytochalsin binds to one end of actin filaments, we could calculate that the spectrin/actin complex probably consists of decamers of polymerized actin cross-linked by spectrin tetramers.

(2) Effect of cytochalasins on actin: The cytochalasin are groups of natural products that are potent inhibitors of a variety of motile processes in eukaryotic cells. This year we observed (a) that the cytochalsins greatly inhibited the rate of polymerization of actin; (b) that cytochalasin D caused rapid depolymerization of F-actin; (c) that cytochalasin D did not depolymerize F-actin when its polymerization had been nucleated by the spectrin/actin complex but does stop further elongation; (d) that the critical concentration of actin was increased by cytochalsin D and (e) that cytochalasins, under appropriate conditions, could accelerate the ATPase activity of polymeric and monomeric actins and disassociate the polymerization of actin from the hydrolysis of ATP.

Considerations of observations (a) through (e) and the previous effects of spectrin/actin complex on actin polymerization have provided strong experimental support for a novel model of actin polymerization which allows for the possibility that there may be net addition of actin monomers at one end of an actin filament and equal net loss of actin monomers at the other end of the actin filament. Thus the system as a whole could be at steady state with neither end of the filament being at equilibrium and with actin monomers moving through the filament from one end to the other. The free energy difference between the ends of the filaments would be provided by the hydrolysis of ATP.

Depolymerization of F-actin by added cytochalasin D and increase in the experimentally measured critical concentration of actin in the presence of cytochalasin D could be explained if cytochalasin D preferentially inhibited events at what would normally be the net polymerizing end of F-actin at steady state. Additional insight into the polymerization process was obtained when we found that cytochalasin D could also greatly stimulate the hydrolysis of ATP by actin even as it inhibited polymerization so that the normally tight coupling between actin ATPase activity and actin polymerization could be uncoupled. All of these data can be fit to one model in which the ATP that is hydrolyzed to ADP and P_i when an actin filament elongates by one subunit may come from the filament and not from the monomer that is being added; i.e., the actin filament may have a terminal bound ATP. Cytochalasin D may interact with that terminal subunit inhibiting the addition of the next monomeric subunit and also catalyzing the hydrolysis of the filament-found ATP.

A number of data suggest that the effects of cytochalasins A, B, C and E on actin polymerization and actin ATPase activity are not identical to those described for cytochalasin D. These drugs will be examined more closely to see if through their use further insights on the actin polymerization mechanism can be deduced. Suggestive evidence has been obtained that monomeric actin may also interact with cytochalasins (in addition to the now-well-described interaction of filament ends with the cytochalasins). This possibility will be further investigated. In order to separate events of the nucleation step from the process of actin elongation, crosslinked dimers of actin will be prepared and used to study the elongation reaction and ATPase reactions of growing actin nuclei. The model proposed above implies, as stated, that at steady state there will be a net addition of actin monomers at one end of the filament and net loss at the other end with the filament length remaining constant. Efforts will be made through the use of radioactively labeled actin to obtain direct evidence for this so-called treadmilling of actin and for the extent to which it is tightly coupled to the hydrolysis of ATP.

Keyword Descriptors: Actin, spectrin, erythrocyte, polymerization, cytochalasin, cytoskeleton

Publications:

Brenner, S. L. and Korn, E. D.: Spectrin-actin interaction. Phosphorylated and dephosphorylated spectrin tetramer crosslink F-actin. J. Biol. Chem. 254:8620-8627, 1979.

Brenner, S. L. and Korn, E. D.: Substoichiometric concentrations of cytochalasin D inhibit actin polymerization: Additional evidence for an F-actin treadmill. J. Biol. Chem. 254:9982-9985, 1979.

Brenner, S. L., and Korn, E. D.: Spectrin/actin complex isolated from sheep erythrocytes accelerates actin polymerization by simple nucleation: Evidence for oligomeric actin in the erythrocyte cytoskeleton. J. Biol. Chem. 255:1670-1676, 1980.

Brenner, S. L. and Korn, E. D.: The effects of cytochalasins on actin polymerization and actin ATPase provide insights into the mechanism of polymerization. J. Biol. Chem. 255:841-844, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00025-05 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James A. Ferretti, Ph.D., Research Chemist,PSL,DCRT
Other: E. D. Becker, Chief, Laboratory of Chemical Physics,LCP,NIAMDD
G. R. Marshall, Professor of Physiology, Department of Physiology and Biophysics, Washington University School of Medicine, St. Louis, Mo.
R. J. Highet, Laboratory of Chemistry, NHLBI
G. H. Weiss, Chief, PSL,DCRT
J. L. Costa, Neuropharmacology Laboratory, NIMH
R. K. Gupta, Institute for Cancer Research, Philadelphia, PA

COOPERATING UNITS (if any)

Laboratory of Chemical Physics, NIAMDD
Laboratory of Chemistry, NHLBI
Neuropharmacology Laboratory, NIMH

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy and also to apply NMR to the study of small proteins. In particular, development of the correlation method of obtaining NMR spectra is of special interest. An experimental and theoretical study of interference effects in correlation spectroscopy has been undertaken. Saturation effects in correlation NMR are currently being studied. Investigations of the solution conformation of derivatives of angiotensin, bradykinin and bleomycin are in progress. In these systems we have demonstrated the importance of the contribution of internal motion to the relaxation behavior.

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

A new 360 MHz NMR spectrometer was purchased and installed in a cooperative project with NHLBI and NIMH. The operation of this spectrometer has involved an extensive training period both in terms of operator use and maintenance. With the availability of this new instrumentation we have initiated a study of complex organic and biological molecules using two-dimensional Fourier transform NMR spectroscopy. The principle advantage of the double Fourier transformation is that fine structure due to spin couplings may be recorded with significantly enhanced resolution. We have thus been able to record spectra of a set of frog toxin isomers as well as the proton spectrum of the antineoplastic agent bleomycin and observe resonances which were previously unresolved. We are currently in the process of attempting to measure two dimensional spectra.

We are continuing to study the magnetic field strength and temperature dependences of the spin-lattice relaxation time, T_1, spin-spin relaxation times, T_2, and nuclear Overhauser enhancement (NOE) factors in biological macromolecules. In addition to investigating various small peptides such as angiotensin-II, gramicidin-S, bradykinin, and various enkephalins, we have also studied a series of polysaccharides. On the basis of these investigations we have developed a method for determining which model for the molecular motion should be used to analyze the relaxation data. From these results we have been able to establish the dependence of the relaxation parameters on the details of the molecular motion and to infer structural parameters in solution. These results have also permitted us to evaluate such models as free internal diffusion, restricted amplitude internal diffusion and multiple internal rotation.

We have extended our study of the molecular complex of Fe(II) and bleomycin to include the pH dependence on the nature of the complex, the association of carbon monoxide with the complex and the interaction of the complex with some oligonucleotides. Bleomycin is a glycopeptide whose iron complex has been shown to be effective against a variety of human neoplasms. The reason for studying the carbon monoxide - Fe(II) - bleomycin complex is that it is stable, diamagnetic, and a structural analog of the active O_2-Fe(II)-bleomycin complex. We are currently synthesizing the carbon monoxide complex with enriched Fe^{57} in order to examine the interaction of the nitrogen ligands with Fe^{57}. On this basis we plan to assign definitively those nitrogen atoms in the bleomycin complex which are ligated to the iron.

We have carried out a comparative solution conformational studies of angiotensin-II and two conformationally restricted analogs by complete assignment of their proton NMR spectra at 600 MHz. The purpose of these studies is to elucidate the receptor-bound conformation by restricting the conformations available and relating these results to biological activity. On the basis of the NMR data we were able to obtain a consistent set of torsional angles for all backbone and sidechain residues in the various analogs.

We are continuing to analyze additional aspects of data reduction in NMR. We are now taking into account the effects of imperfections and inhomogeneities in the rf pulses on the determination of spin-lattice relaxation times, T_1. We have determined the optimum pulse spacings when T_1 and the equilibrium magnetization are unknown and the effective flip angle generated by an rf pulse is determined in a separate experiment. We are also considering the more general three-parameter problem. We have also developed a method for estimating the variance in the measurement of chemical shifts in the presence of experimental noise. We consider cases in which the data are obtained by the CW method where the noise is uncorrelated and also cases in which the spectra obtained by Fourier transform method where the noise may contain correlations.

Keyword Descriptors: Nuclear magnetic resonance, angiotensin, bleomycin, correlation method

Publications:

Weiss, G. H., Gupta, R. K., Ferretti, J. A., and Becker, E. D.: The choice of optimal parameters for measurement of spin-lattice relaxation times. I. Mathematical formulation. J. Magnet. Resonance 37:369-380, 1980.

Becker, E. D., Ferretti, J. A., Gupta, R. K., and Weiss, G. H.: The choice of optimal parameters for measurement of spin-lattice relaxation times. II. Comparison of saturation-recovery, inversion-recovery, and fast inversion recovery experiments. J. Magnet. Resonance 37:381-394, 1980.

Ciarkowski, J. E., Ferretti, James A., and Marshall, G. R.: Comparative conformational studies of Angiotensin II and two sterically constrained analogs by 600 MHz proton NMR spectroscopy. Journal of the American Chemical Society (in press).

Gupta, R. K., Becker, E. D., Ferretti, J. A. and Weiss, G. H.: A variable perturbation method for nuclear spin-lattice relaxation measurements. J. Magnet. Resonance 35:301-306, 1979.

Becker, E. D., Ferretti, J. A. and Gambhir, P. N.: Selection of optimum parameters for pulse Fourier transform Nuclear Magnetic Resonance. Anal. Chem. 51:1413-1420, 1979.

Ciarkowski, J. E., Ferretti, J. A., and Marshall, G. R.: Comparison of Angiotensin I and two sterically constrained analogs by 600 MHz proton NMR. Fed. Proc. 39:1946, 1980.

Gupta, R. K., Ferretti, J. A., Becker, E. D. and Weiss, G. H.: A modified fast inversion recovery technique for spin-lattice relaxation measurements. J. Magnet. Resonance (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00021-09 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Correlation Function Spectroscopy/Laser Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Ph.D., Research Physicist, PSL, DCRT

COOPERATING UNITS (if any)

J. Gladner, Ph.D., LBC, NIAMDD
R. Bonner, Ph.D., BEIB, DRS;
H. T. Pretorius, M.D., CEB, NIAMDD; & P. D. Bowen, LTD, NHLBI.

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental and theoretical studies have been performed to develop laser inelastic light scattering methods for studying biological gels, viscoelastic polymer solutions and other materials. Studies also are being performed in order to understand how laser Doppler techniques can be used to measure capillary blood flow in tissues.

PHS-6040
(Rev. 10-76)

Correlation Function Spectroscopy/Laser Light Scattering

The primary objective of this project is development of laser inelastic light scattering techniques for performing rapid and precise measurements on biological systems and materials. In principle, any process giving rise to refractive index fluctuations can be monitored. The instrument which we have constructed has been used to measure diffusion coefficients of macromolecules, swimming speed distributions of motile microorganisms, elastic moduli of gels and blood flow in capillaries.

Recent emphasis has been on understanding inelastic light scattering processes relating to blood flow in tissue microvasculature (with R. Bonner, BEIB). A theory has been developed to account for the facts that the tissue matrix which surrounds the blood cells is a strong diffuser of light, and that multiple interactions of photons with moving cells results in spectral sensitivity to changes in blood volume. Theoretical predictions have been verified by measurements of particle flow through model tissues (with P. Bowen, NHLBI). These studies were undertaken to support efforts being made by personnel in BEIB and NHLBI who are developing a laser Doppler instrument to measure peripheral blood flow. The basic operation of the flowmeter now seems to be understood, but we anticipate additional collaborative studies arising from experience gained in clinical applications.

Another part of this project concerns development of non-invasive quasi-elastic light scattering schemes for measuring mechanical properties of viscoelastic media and dilute polymer networks. One scheme involves inducing small amplitude shear waves in gels which are formed in light scattering cuvettes of particular geometry, and then measuring the frequencies of intracavity elastic waves. During the past year theoretical and laboratory studies were undertaken to extend previously developed techniques to new sample geometries. Also, a scheme has been devised to measure parameters which characterize the inelastic damping of shear waves arising from transient molecular rearrangements of gel constituents. Modifications necessary to apply similar techniques to viscoelastic polymer solutions have been investigated, and we have continued studies regarding the relationships between composition and mechanical rigidity of fibrin clots (with J. Gladner, NIAMDD).

Keyword Descriptors: Laser light scattering, macromolecules, diffusion coefficients, correlation functions, gels, blood flow.

Publications:

Gelman, R. W., Gladner, J. A. and Nossal, R.: The rigidity of fibrin gels as measured by quasielastic light scattering. Biopolymers 19: 1259-1270, 1980.

Bonner, R. and Nossal, R.: A model for laser Doppler measurements of blood flow in tissues. Applied Optics (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00017-08 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cell Motility and Chemotaxis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Research Physicist, PSL, DCRT

COOPERATING UNITS (if any)

L. Lipkin, M.D., DCBD, NCI

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0.2	0.2	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been undertaken to study various aspects of cell locomotion, including the mathematical basis of macroscopic assays to leukocyte chemotaxis. New procedures for measuring parameters of cell migration, including computer assisted tracing techniques, are being developed. Mathematical relationships between microscopic cell motion and macroscopic response are derived.

Cell Motility and Chemotaxis

This study relates to cell locomotion and chemotaxis. Recent emphasis has been on examining certain immunologic aspects of leukocyte migration.

As part of this project, a general mathematical theory for interpreting results of capillary migration assays for cellular immune sensitivity (MIF tests) was derived. However, various basic parameters of leukocyte movement which are necessary for quantitating the assay are not well known. Consequently, collaborative experiments were performed with Dr. Lewis Lipkin (DCBD/NCI) which involved studying the response of neutrophils to various chemical factors ("lymphokines") produced by stimulate lympocytes. Much of the acquired data is recorded on 16mm time-lapse motion picture film. A scheme has been developed for creating computer data sets of cell positions, which involves reading the films by a television monitor which is connected to a specially-designed computer having a densitometer input. Algorithms and computer programs have been devised to process these data, in order to study details of microscopic stochastic locomotion of the leukocytes. Ultimately, these techniques will be used to examine the behavior of neutrophils when responding to chemoattractants.

To support these studies, a general review of mathematical work on chemotactic response was prepared. Subsequently, a quantitative relationship between binding of chemoattractant to the surface of bacteria and the resulting mean chemotactic response velocity of the cells was elucidated.

Keyword Descriptors: Cell locomotion, leukocyte chemotaxis, capillary migration assays.

Publications:

Nossal, R.: Mathematical Theories of Topotaxis. Proceedings of the Conference on Biological Growth and Spread Models. Heidelberg, Germany, Springer-Verlag (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00026-05 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Theory and Measurement of Intermolecular Forces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	V. A. Parsegian, Ph.D., PSL, DCRT
	G. H. Weiss, PSL, DCRT
	A. N. Schechter, LCB, NIAMDD
	M. Prouty
Others:	R. P. Rand, Brock University
	L. Lis, Brock University
	N. Fuller, Brock University
	M. Loosley-Millman, University of Guelph

COOPERATING UNITS (if any)

Laboratory of Chemical Biology, NIAMDD

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2.3	2.0	0.3

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

During the present year we have been able to quantify intermolecular forces involving several kinds of phospholipid bilayer membranes. The forces of interest act between membranes as well as between molecules in the same bilayer. There appears to be close analogies between forces involving lipids and those stabilizing aggregates of proteins and nucleic acids.

The experimentally decaying "hydration forces" which dominate bilayer repulsion below 30Å separation are seen to depend both in magnitude and decay rate, on the chemical identity of other groups on the bilayer surface. A rationale is now apparent for the activity of enzymes that modify these groups and reside on the bilayer surfaces of naturally occurring residues.

Electrostatic forces are observed between bilayers charged by the adsorption of ions or by inclusion of charged phospholipid species. These forces extend beyond the 30 Å reach of the hydration force. Their exponential decay is of the magnitude expected for electrostatic forces screened by ionic solutions.

PHS-6040
(Rev. 10-76)

Theory and Measurement of Intermolecular Forces

Studies with Professors Peter Rand and Leonard Lis have revealed several classes of forces between phospholipid bilayer membranes. These include several estimates of the van der Waals force between bodies in water. The results published so far are a series of systematic studies on the physical properties of cell membrane lipids.

From observations on a wide variety of phospholipids and phospholipid/cholesterol mixtures, it is clear the dominant force between membranes that are stable in water is due to the work of removing water from between their approaching surfaces. These forces die off exponentially and are independent of electric charge on the membrane surface. In natural systems it poses a final and imposing barrier to contact between different membranes.

Electrostatic interactions have been measured between bilayers composed of charged phospholipids as well as between bilayers charged by the adsorption of ions. In the former case these forces follow approximately the behavior expected from double layer theory. In the latter case, bilayer electrostatic repulsion is much slower than expected. The deviation is ascribed to progressive desorption of ions as bilayers approach. So different is ion adsorption to phosphatidylcholines of different side chains that mixtures actually separate into different lamellar phases, probably a result of different degrees of charging of different species. Alkaline earth ion bonding depends on ion type as well as on specificity and packing of the phospholipid molecules.

Techniques similar to those used to measure forces among lipids are being applied to determine protein interactions. It has been shown that deoxygenated sickle cell hemoglobin can be forced into a gel state by the same osmotic stress method used to push bilayers together. We can, in this way, measure the energetics of gelation and determine the influence of temperature and liganding species.

Keyword Descriptors: Phospholipid bilayer membranes, hydration forces, electrostatic forces, ionic solutions.

Publications:

Lis, L. J., Rand, R. P. and Parsegian, V. A.: Measurement of the adsorption of Ca^{++} and Mg^{++} to phosphatidyl choline bilayers. In Blank, M. (Ed.): *Bioelectrochemistry: Ions, Surfaces and Membranes*. American Chemical Society, Washington, D. C., 1979, 173-179.

Parsegian, V. A., Fuller, N. and Rand. R. P.: Measured work of deformation and repulsion of lecithin bilayers. *Proc. Natl. Acad. Sci. USA* 76, 2750-2754, 1979.

Parsegian, V. A.: Competitive forces influencing the interaction of biological cells. In Berg, J. (Ed.): Proceedings of the Feb. 1979 Workshop on Interfacial Phenomena. University of Washington, Seattle, 214-217.

Parsegian, V. A., Rand, R. P., Fuller, N., McAlister, M., Lis, L. J.: Molecular forces between and within lipid membranes. Biorheology 16: 293-295, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00024-05 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Studies in Mathematics and Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	George H. Weiss, Ph.D., Chief, PSL, DCRT
Other:	J. E. Kiefer, Research Mathematician, PSL

COOPERATING UNITS (if any)

R. J. Rubin, Senior Scientist, NBS
K. E. Shuler, Ph.D., University of California, San Diego
K. E. Lindenberg, Ph.D., University of California, San Diego

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0.6	0.4	0.2

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This year has seen the completion of several projects related to polymer configurations as modelled in terms of random walks. A start was made on a comprehensive review article on applications of random walks in chemical physics.

PHS-6040
(Rev. 10-76)

Studies in Mathematics and Statistics

We have completed several studies on random walk models applied to problems in energy transfer in different materials. These models arise naturally in the study of processes such as photosynthesis in which light energy excitations move by diffusion until reemission occurs. A large amount of time was spent on a review article on random walks, which is approximately half done.

Keyword Descriptors: Random walks, diffusion of energy.

Publications:

Bunow, B., Weiss, G. H.: How chaotic is chaos? Chaotic and other "noisy" dynamics in the frequency domain. Math. Biosci. 47:221-237,1979.

Weiss, G. H.: A note on occupation times of random walks. J. Stat. Phys. 21:609-611, 1979.

Weiss, G. H., Rubin, R. J.: Internal configurations of span-constrained random walks. J. Stat. Phys. 22:97-109, 1980.

Lindenberg, K., Seshadri, V. E., Shuler, K. E., Weiss, G. H.: Lattice random walks for sets of random walkers. J.Stat. Phys. (to appear).

Dishon, M., Weiss, G. H.: Small sample comparison of estimation methods for the beta distribution. Journal of Statistical Computation and Simulation 11:1-12, 1980.

Weiss, G. H.: First passage time problems for one dimensional random walks. J. Stat. Phys. (to appear).

Weiss, G. H.: Asymptotic form for random walk survival probabilities on 3-D lattices with traps. Proc. Natl. Acad. Sci. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Interaction of Cell Surface Proteins with the Cytoskeleton

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT
Other: B. Bowers, Ph.D., NHLBI

COOPERATING UNITS (if any)

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental studies have been performed to develop an electronmicroscopic method to detect cytoskeletal proteins located under cell membranes. This method will be used to examine quantitatively the interaction of cell surface proteins with the cytoskeletal elements and its importance in the physiology and function of the cells.

PHS-6040
(Rev. 10-76)

Interaction of Cell Surface Proteins with the Cytoskeleton

Membrane proteins can interact with various components inside the cell, e.g., cytoskeletal elements. We have looked for possible physical mechanisms to account for the attachment of membrane proteins to cytoskeletal filaments e.g. by entanglement or by polymerization of cytoskeletal elements around aggregated membrane proteins.

There are some indications, on the visible light microscopical level, that these cytoskeletal structures are affected by changes in the location of cell surface proteins. We have developed an electron microscopic method that makes it possible to observe these structures inside the cell. In order to enhance the visibility of the cytoskeletal microfilaments we use the Evans & Sutherland facilities for image display and analysis. With this method we plan to quantitate the amount and morphology of cytoskeletal elements. In doing so, changes in the cytoskeleton will be detected and correlated with changes in cell surface proteins. These studies might shed light on how signals are transferred through membranes to cell interiors.

Keyword Descriptors: Electron microscopy, cell surfaces, membrane proteins, cytoskeleton.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT 00067-01 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analysis of the effects of cytocholasin B and D on the distribution of groups of insulin receptor sites on rat adipocytes.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT
Other:	L. Jarett, Head, Departments of Pathology and Laboratory of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
	R. Smith, University of Pennsylvania School of Medicine, Philadelphia, PA

COOPERATING UNITS (if any)

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In this study the distribution of insulin binding sites on the surface of rat adipocytes was studied using monomeric ferritin-insulin viewed by electronmicroscopy and analyzed by newly developed quantitative methods. This analysis shows that insulin binding sites are non randomly distributed on rat adipocyte plasma membrane. The quantitative characteristics of the receptor groups (e.g. distances between the sites) and the mode of action of cytochalasin B has been elucidated.

PHS-6040
(Rev. 10-76)

Analysis of the effects of Cytocholasin B and D on the distribution of groups of insulin receptor sites on rat adipocytes

The binding of hormones to their receptors on cell membranes is believed to be the first step in their biological action. Insulin binding sites appear in groups on the plasma membranes of rat adipocytes, as visualized electronmicroscopically with monomeric ferritin-insulin particles (Fm-I), and cytochalasin B(CB) but not cytochalasin D(CD) partially disrupts these groups (J. Clin. Invest. 63:571, 1979). The present study used computer analysis of the spatial distribution of Fm-I to quantitate and characterize more objectively the effects of CB and CD on Fm-I groups. Fm-I were non-randomly distributed in the presence or absence of CB or CD. By computational definition a group included consecutive Fm-I separated by less than 200, 300, 400, 500 or 600 Å. At the 200 Å limit, large groups (5 Fm-I) were twice as abundant in the absence as presence of CB whereas single Fm-I and pairs were 26% and 28% greater with CB, indicating that CB disrupted groups. The relative change by CB action in distribution of Fm-I in groups of 1, 2, and 5 was not affected by the defined separation distance (at least up to 600 Å). On control and CB treated cells the distance between adjacent Fm-I particles in a group do not appear to exceed 400 Å. Thus CB appears to disrupt portions of groups of insulin binding sites of all sizes without regard to distances between adjacent receptor sites within a group. Computational analysis of morphological studies on insulin and other receptors should provide more information than visual analysis.

Keyword Descriptors: Insulin binding sites, insulin receptors, cytochalasin B, membrane proteins electron microscopy.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00041-02 PSL

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Quantitative Analysis of the Electronmicroscopy of cells and their Plasma Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N. D. Gershon, Ph.D., Visiting Scientists, PSL,DCRT
Other:	R. Nossal, Ph.D., Research Physicist, PSL,DCRT
	K. Porter, Ph.D. Head, High Voltage Electron Microscope Unit, Department of Molecular, Cellular & Developmental Biology, University of Colorado, Boulder, Colorado
	T. Triche, M.D., Ph.D., NCI
	B. Bowers, Ph.D., NHLBI
	M. Weissberger, Ph.D., PSL, DCRT

COOPERATING UNITS (if any)

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods of quantitative electronmicroscopy of protein particles on membranes were developed and applied to the analysis of cancer cells infected by viruses, and intramembraneous particles. A computerized approach to autoradiography has been developed and which will be applied to analyze the localization of IgE receptors on most cell membranes. A study of the three dimensional structure of polymerization centers for macromolecules in cells has been initiated.

Quantitative Methods in Electronmicroscopy

We have developed quantitative methods to analyze electronmicrographs of biological systems. The methods includes digitization of micrographs and computational analysis of their contents (e.g. protein particles on membranes).

(a) For a virally infected cancerous cell we have found that the viral glycoproteins are distributed in a non-random fashion on the cell surface even at temperatures where the viral bonds cannot be formed. Studies of intramembranous particles in a mouse fibroblast and of a gap junction showed that the particles were almost randomly distributed in the former and distinctly non-randomly distributed in the latter. This work was done in collaboration with Dr. A. Demsey.

(b) The localization of receptor sites on membranes are carried out by autoradiographic methods. The analysis of the resulting micrographs is usually done manually which is extremely cumbersome and slow. The use of a digitizer and the computing facilities at DCRT will enable a fast and accurate analysis of autoradiographic results. It will be used to analyze the localization of IgE receptors on most cells. This work is done in collaboration with Dr. T. Triche and with G. Weiss.

(c) A three dimensional arrangement of some cell organelles is important to cell function. At the present time electronmicroscopy is the only method available to visualize microfilaments, microtubules and cell membranes at sufficient resolution to study their arrangement and interrelationships. Using electronmicrographs produced by the high voltage electronmicroscope (a national resource sponsored by NIH) in Boulder, Colorado, the new digitizing system being constructed at PSL and the computational facilities at DCRT, the three dimensional location of organelles in cells are measured and their structure is going to be elucidated. This will shed light on what determines and maintains cell form in normal and malignant cells. This work is done with R. Nossal, K. Porter, B. Bowers and M. Weissberger.

Keyword Descriptors: Electron microscopy, high voltage electronmicroscopy, digitization of micrographs, cell surfaces, membrane proteins, microfilaments, cytoskeleton, autoradiography.

Publications:

Gershon, N. D., Demsey, A., Stackpole, C.: Analysis of local order in the spatial distribution of cell surface molecular assemblies. Exp. Cell Res. 122:115-121, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00068-01 PSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Diffusion of Molecules on Cell Surfaces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT
Other:	B. Aizenbud, Chemistry Department, Ben Gurion University, Beer Sheva, Israel

COOPERATING UNITS (if any)
Chemistry Departmemt, Ben Gurion University, Beer Sheva,

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Division of Computer Research & Technology

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

SUMMARY OF WORK (200 words or less - underline keywords)

A theoretical study was carried out to determine the role of cell surface curvature on the observed diffusion rate of membrane proteins using fluorescence photobleaching recovery. For the particular surface used which has a similar geometry to natural microvillous membranes, it was found that the assumption that the membrane is planar does not affect the calculated diffusion constant to a large extent.

PHS-6040
(12-75)

Diffusing of Molecules on Cell Surfaces

Fluorescence photobleaching recovery (FPR) techniques have been used to study lateral movement of molecules on membranes. Fluorescent molecules within a circular spot are bleached and the time dependence of the fluorescence recovery in the spot is measured. The physical interpretation of these results in terms of diffusion along the membranes is based on the assumption that the surface is planar. However, biological membranes may be nonplanar, e.g., they may have blebs and microvilli. To study the effect of nonplanarity on the diffusion rate, the diffusion equation along curved surfaces was derived. This equation was employed in studying the diffusion along a "wavy" surface of the form Acos(kx)cos(ky). The numerical calculations show that for k=10 (um)$^{-1}$ and a bleached spot of 1 um in diameter, the time dependence of the intensity of fluorescence in the bleached spot depends on A at low values of A(0,.1 and .5um) while the dependence on A at higher values of A (.5 compared with 1 and 2 um) is weak. Assuming that the membrane is planar, the interpretation of FPR measurements might yield a diffusion constant which is 40% (for A=1) of the real diffusion coefficient along the curved surface. These results suggest that the transition from a plane to a surface with small microvilli slows the diffusion process while the transition from small to large microvilli practically does not affect the diffusion rate of molecules to and of the bleached area.

Keyword Decriptors: Membrane proteins mobility, lateral diffusion, microvilli, fluorescence photobleaching recovery.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00066-01 PSL

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Computerized Typesetting of Scientific Papers

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A. Parsegian, Ph.D., PSL, DCRT
Others: N. Crawford, PSL, DCRT
M. Douglas, Computer Systems Analyst, LAS, DCRT
M. Horton, Computer Systems Analyst, LAS, DCRT
P. Miller, Information Officer, OD, DCRT
R. McElroy, Applications Specialist, Graphic Systems Division, GPO
M. McNeel

COOPERATING UNITS (if any)

Science Press, Biophysical Journal

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology

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CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The aim of this project is to simplify and make cheaper the publication of scientific articles. We can convert electronically texts typed on word processor or computer text editors and sorted on magnetic media into tapes that can be used to direct computer typesetting systems. Already, such materials have been used to create WYLBUR files wherein the texts are modified to direct formating according to the requirements of publisher and printer. Magnetic tapes of manuscripts are produced and sent with the paper copy to scientific journals. Expensive, error-prone rekeyboarding at the printing plant is eliminated. All the care invested in a final typescript is not lost. Time is saved. Galley proof-reading is substantially simplified. Total typesetting costs can be halved.

After demonstration of this method's utility, it is reasonable to request sharing of savings between publisher and government by significant reduction of page charges. Given the near ubiquity of computerized composition, one can expect virtually all journals used by NIH authors to be amenable to the new procedures. The software, once developed, is easily transformed for general use on other computer systems outside the NIH.

Computerized Typesetting of Scientific Papers

It has been shown that the magnetic memory storage from a word processor or file from a computer text editing program can be read into the WYLBUR system to be converted into a magnetic tape to be fed to a typesetting computer. In our initial experiment a tape was produced of material typed into WYLBUR by Nancy Crawford. A test tape was successfully "hung" to create a galley proof of the material. The tape writing program was the work of B. Douglas. Next, a full paper, by John Fletcher, of LAS, DCRT which was already typed on WYLBUR was converted to tape and set to type to appear in the March 1980 Biophysical Journal. The extended tape writing program for this step was the work of M. Horton and B. Douglas.

Since that time over a dozen papers have been read into WYLBUR either from local communicating word processors or by telephonic transmission. A full set of galleys, produced from material funnelled into WYLBUR was produced in April 1980 to create the pre-meeting Study Book for a meeting on "Proteins and Nucleoproteins: Structure, Dynamics and Assembly".

Cost saving of at least 50% are expected of this new method. Speed in publication and minimization of errors due to retyping are additional virtues. Systematic programming is now under way to write programs to create magnetic tapes to accompany all NIH articles sent to printers for publication. It should soon be possible to realize significant reductions in page charges for NIH research publications.

The DCRT Information Office prepared a booklet as a test using these direct typesetting methods; three more booklets are being prepared this way.

Keyword Descriptors: Computer typesetting, WYLBUR, Computerized composition.

Publications: None

Office of the Director FY 1980 Projects

Arnold W. Pratt, M.D.
DCRT Director

Natural Language Access to Clinical Data Bases

M. N. Epstein. The objective of this project, begun in FY77, is the development and evaluation of a system that will provide physicians access to medical data through natural language queries to support both patient management and clinical research. In FY80 a collaborative project began to develop two data bases each containing data on 500 patients with malignant melanoma. The project uses the MEDINQUIRY system and involves scientists at the University of California at San Francisco, the University of Pennsylvania, and SRI International. The project moved from DCRT to the Lister Hill Center, NLM when M. N. Epstein accepted a position as Assistant to the Director of the Center.

Library Automation

E. Chu; J. Mahaffey (DMB); J. Knight (CSL). In FY78 work began with DMB on a new automated circulation system for the DCRT Library. It went into operation in FY79, with new indices for the document collection (authors and keywords in title) added in FY80. In FY80 the DCRT Librarian worked with CSL staff as consultants to the NIH Library in its automation program. Some effort also went into exploring implications for the DCRT Library of automation by the Library of Congress (particularly its online catalog) and of changes in the Anglo American Cataloging rules.

DCRT Publication File

P. O. Miller; R. Baxter (DMB). In FY79 the Information Office began to create a file of citations for all papers published by DCRT authors. In FY80 the file and its maintenance programs were established and work began on programs for standard reports.

DCRT Information Program

P. O. Miller; W. C. Mohler. This is an ongoing project to develop a coordinated information program for DCRT. It has four parts: Analyzing Needs, Creating and Evaluating Products, Developing Resources, and Education. Special emphasis in FY80 fell on developing products to fill some existing needs and in arranging new courses in communication techniques for DCRT employees.

Who at NIH uses DCRT for what?

W. C. Mohler; L. L. Manuel. DCRT services support activities throughout NIH for more than 3,000 registered users on some 1.100 accounts. A survey in FY79 asked users to categorize the types of NIH activities supported by each account in the previous year. The same survey made again in FY80 showed a substantial variation in the categories chosen to describe many individual accounts. A new survey instrument will be used in FY81 in an effort to reduce the "noise" in the survey results and provide the basis for more reliable analysis of the data.

Clinical Data Management and Analysis

W. C. Mohler; J. R. Shapiro (Clinical Center). Inspite of the rapid growth in use of data management and statistical packages provided for NIH scientists on DCRT computers, there is a perceived need for facilities that would be easier to learn and use in NIH clinical research projects. In FY80 a pilot project began to evaluate this need and specify a system or systems to meet the need if it proves substantial.

Multi-function Microprocessor Interface

A. W. Pratt; D. Songco (CSL). The project begun in FY80 seeks to adapt a variety of information acquisition techniques on a single micro computer as versatile data input/output interface for biomedical scientists and clinicians.

Medical Linguistics

A. W. Pratt, et al. This is a long term project to define a set of semantic and syntactic forms that can aid in the analysis and interpretation of written medical statements.

Image Processing, Decision Analysis and Computer Architectures

J. M. S. Prewitt. (Summaries for projects in this group of activities were not available in FY80.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01-CT-00038-03 OSTC/OD

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Natural Language Access to Clinical Data Bases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Martin N. Epstein, Scientist, OD, DCRT

COOPERATING UNITS (if any)

SRI International	Menlo Park, California 94025
University of California	San Francisco, California 94143
University of Pennsylvania	Philadelphia, Pennsylvania 19104

LAB/BRANCH

Office of the Director

SECTION

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Division of Computer Research and Technology

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SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this research is the development and evaluation of a system, called MEDINQUIRY, that will allow medical scientists direct access to patient medical data through natural language queries to support both patient management and clinical research.

A prototype MEDINQUIRY system has been implemented for a small data base on malignant melanoma. The physician can enter queries in English that retrieve specified data for particular patients or for groups of patients satisfying certain characteristics, that perform simple calculations, that allow browsing through the data base, that provide information about the data base, and that assist in hypothesis formation and testing.

Natural Language Access to Clinical Data Bases

Objectives:

1. Develop a natural language question answering facility that will provide a direct and convenient interface between an expert and a computerized data base of patient data on specific diseases to support patient management and clinical research.
2. Collect and maintain in machine readable form multiple data bases of clinical and histological data on patients with malignant melanoma.
3. Identify classes of requests that physicians wish to ask of a clinical data base and develop methods to respond to these requests.
4. Build an application language that contains both domain specific knowledge about melanoma and general knowledge about language that will allow understanding English language requests formulated by clinicians, researchers, and health professionals.
5. Gain insights into the medical inquiry process, using an information processing approach, to model how experts pose questions.
6. Evaluate the effects of using the system to aid the physician in patient management and in more precisely studying the clinical course of the disease.

Methods:

A system called "LIFER", developed at SRI International, provides a facility that allows a language interface builder (in this case the PI) to specify rules required to process English language query requests. These rules are used to specify the application vocabulary, grammar rules, and data base interface functions. These tasks can be accomplished online and modifications can be made rapidly and immediately tested. Special purpose facilities available include an ellipsis capability to process incomplete requests, a spelling corrector, a pronoun reference facility, and a paraphrase mechanism that allows the aggregation of data base attributes and the definition of meta questions. Using the pronoun reference facility, a requestor can follow a line of inquiry to test a particular hypothesis by entering a sequence of requests that depend on each other.

Findings:

1. The methods applied provide a stepwise facility for determining the classes of questions that physicians desire to ask of a clinical data base.

2. Through use of the English language access facility hypotheses on melanoma that have been established in the literature can be confirmed and new hypotheses can be formulated and tested.

3. The availability to physicians of online English language access has encouraged a more active interest and participation by physicians in the data acquisition process, in completing missing values in the data base, and in actively perusing the information in the data base.

4. Using the paraphrase facility, it is possible for experts to formulate requests about recurrence and survival on a yearly basis for specified groups of patients.

5. The problem of providing linguistic and conceptual coverage for requests posed to the system is a difficult one. Not only must MEDINQUIRY recognize a wide variety of syntactic and semantic constructs from a user perspective, it must also possess knowledge about the attributes and values recorded in the data base. Each expert using the system has a different point of view of what information should be in the data base and what questions can be asked. To make for smoother immediate use, it may be necessary to provide some description to the user of the basic classes of questions that can be processed. MEDINQUIRY currently contains an application vocabulary of over 900 words and close to 1700 rules. The process of augmenting the application language and enhancing the linguistic and conceptual coverage of the system is a continuing one.

6. MEDINQUIRY has been demonstrated to physicians who are specialists in melanoma, other cancers, and a variety of other diseases. The reactions have been uniformly positive, even though the existing data base is not large enough to provide significant results. The ability to formulate queries in ordinary English and to have the results displayed immediately is extremely appealing. The facility for correcting spelling errors received special commendation.

Proposed Course:

1. A collaborative project involving the University of California, San Franscisco (UCSF), the University of Pennsylvania, and SRI International began in September 1979. This involves creating two larger data bases of 500 patients each on patients with malignant melanoma; one at UCSF, and one at Pennsylvania. These data bases will allow the use and evaluation of the MEDINQUIRY system by experts at these institutions as well as extending the linguistic and conceptual coverage of the system.

2. Expand the current knowledge base, that is the application language, to include expert defined higher order concepts and thus reflect the current state of medical understanding of the disease. A knowledge base also would contain rules for understanding the context of requests and developing appropriate prompts and paraphrase capabilities that show a greater degree of understanding of the medical domain.

3. Extend the data base management facility to provide more efficient access, and provide better capabilities for the presentation and display of the results of inquiry.

4. Evaluate the use of the system by physicians and study the requirements for adapting the system for different diseases and on other computer systems. In particular, it is planned to compare a key word and/or menu tree search strategies with the English language access to determine the advantages and disadvantages of each approach in providing experts with convenient access to their data.

Potential Significance to Biomedical Research:

1. Provide convenient access to medical data bases to allow physicians to browse through their data and more adequately formulate and test hypotheses about the clinical course of a disease. In particular, it should provide support for assessing prognosis and planning therapy.

2. Assist the clinical investigator in identifying and studying relationships among data attributes.

3. Study the process of medical inquiry to better model how experts pose questions. This may provide systems better suited to support decision making in medicine.

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